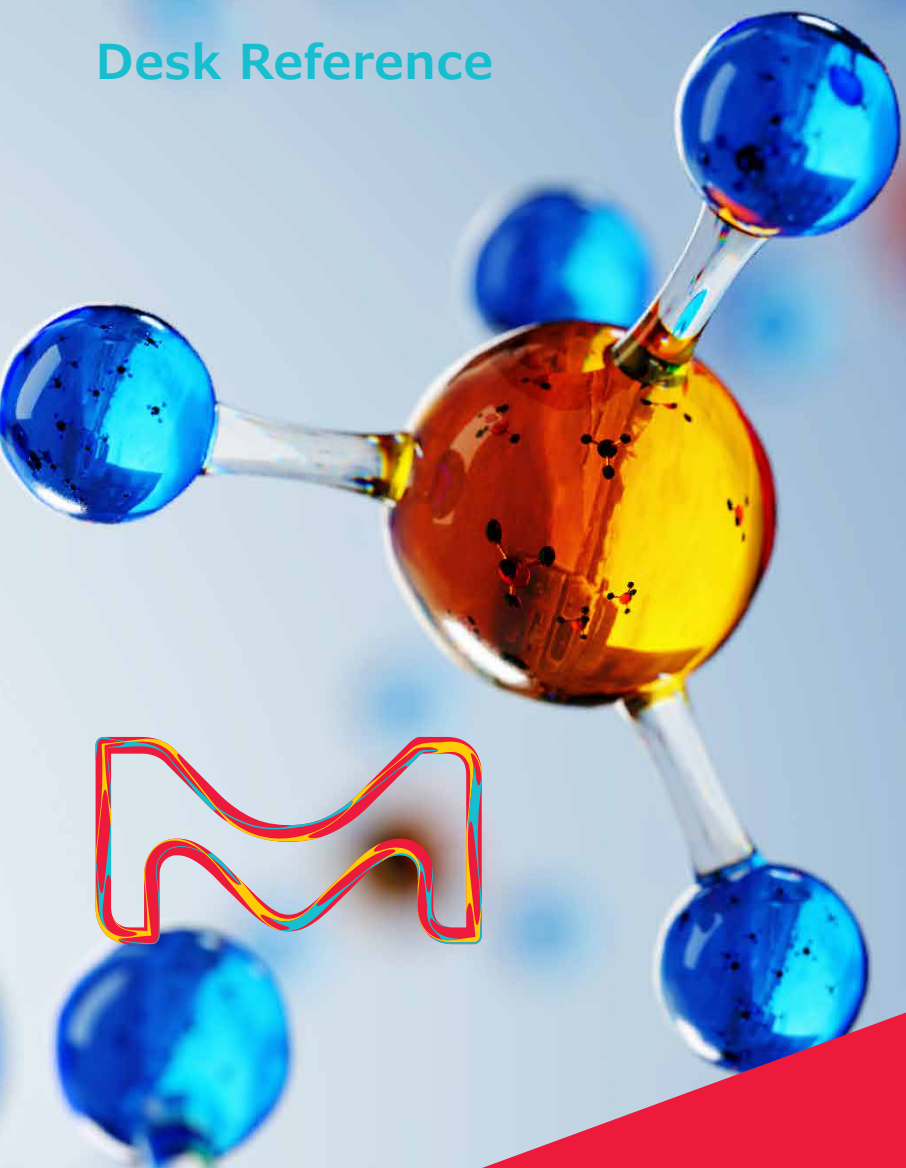
C–H Functionalization Reaction Manual

Desk Reference



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Foreword

C–H functionalization has been called[1] the holy grail of synthetic organic chemistry. The reliable and predictable conversion of a C–H into a C–C, C–N, C–O, or C–X bond in a selective and controlled fashion represents a host of benefits in terms of step economy and waste reduction, driving the current energetic pace of research in this area. The challenges for inventing these aspirational processes are vast, requiring the design of sophisticated new catalyst systems and the development of novel reaction mechanisms. However, a different kind of challenge becomes apparent when seeking to apply these methods to chemical synthesis.

As organic chemists, we are taught to approach the construction of a target molecule through the lens of retrosynthesis. We look for familiar structural or functional group patterns that offer clues to potential routes for their synthesis. Whether it is the alpha-hydroxy carbonyl aldol product, the cyclohexene Diels–Alder product, or the alkene Wittig product, these molecular handles guide our thought processes in designing strategies. This mode of thinking also informs practitioners as to the part of a molecule that will undergo a given reaction in the forward direction, an aldehyde or ketone for the aldol or Wittig reactions or a diene/dienophile for the Diels–Alder reaction. C–H functionalization does not fit this mode of thinking. Functionalization of a C–H bond can frequently occur in a fashion that leaves few structural clues, a characteristic that is often considered a benefit of this chemistry. The factors that determine the site of reaction in a substrate containing a multitude of C–H bonds, all with relatively similar bond dissociation energies, are both subtle and quite different to those operative in the established language of synthetic organic chemistry. This is the basis of one of the great challenges to C–H functionalization being widely adopted by synthetic organic chemists: it requires operating by a different set of rules.

While fully understanding and predicting the site or sites of reactivity from the host of C–H bonds in a given organic molecule remains a highly active and constantly developing field, several trends and guidelines have emerged that the nonexpert can use to direct C–H functionalization chemistry applications in a predictable and robust way. The aim of this manual is to provide a starting point for the uninitiated synthetic organic chemistry practitioner who is interested in using this powerful technique. We hope readers will gain through this manual an understanding of the scope and limitations of a technique and be provided with a set of common conditions to assess the feasibility of their specific substrate. Partnering with MilliporeSigma allows us to provide this knowledge alongside an easily accessible list of materials and resources that should streamline entry into performing this chemistry.

The wealth of transformations that have been developed in the field of C–H functionalization makes comprehensive analysis of the multidimensional factors that govern selectivity in each case beyond the scope of this manual. Instead, we have selected a cross section of reactions to provide an entry point for new users. As authors, we hope this reference will inspire others to unify trends and observations into future volumes of this manual. Our goal is to provide comprehensive coverage of this field and facilitate adoption of this transformative technology.

Introduction: From Traditional Reactivity to Confident C–H Functionalization

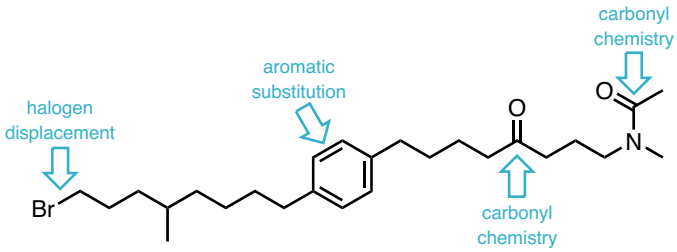
Retrosynthetic analysis, the powerful means by which synthetic organic chemists mentally dissect molecules into readily available starting materials, has traditionally relied on both an intimate understanding of the reactivity of functional groups and a large vocabulary of possible reactions that these functional groups can undergo. This functional-group centered strategy arose from necessity: as methods to selectively address specific C–H bonds were elusive, the only way to assemble complex molecules was through the idiosyncratic reactivity of such stalwarts as the carbonyl, alkene, and other synthetic handles. However, recent efforts across organic chemistry, organometallics, and catalysis have made serious inroads in both understanding the reactivity of C–H bonds and developing robust reactions taking advantage of this insight, suggesting that the time is right to widely introduce these tactics to the retrosynthetic lexicon.[2]

An illustration of the complementarity of C–H functionalization to traditional, functional-group centered reactivity is provided by the example molecule in **Figure 1**.

C–H functionalization not only expands the number of sites that can be targeted in a given molecule, multiplying the opportunities for elaborating it into a more complex product, but it also allows for completely different kinds of chemical bonds to be targeted, often with high chemoselectivity. Working in tandem with traditional functional-group chemistry, C–H functionalization provides the potential to greatly streamline chemical synthesis.

Many researchers at the cutting edge of synthetic chemistry have already recognized the opportunities afforded by selective C–H functionalization for the construction of complex natural products and pharmaceutical compounds. From the numerous examples of C–H functionalization in complex synthesis, the Du Bois enantioselective synthesis of (-)-tetrodotoxin is notable for showing the ability of these strategies,[3] particularly a bold late-stage C–H amination (**Figure 2**), to dramatically truncate the length of synthetic schemes, reducing the longest linear sequence of their synthesis to 34 steps from the previous shortest route of 68 steps.[4]

Conventional Functional-Group Based Reactivity



C–H Functionalization Based Reactivity

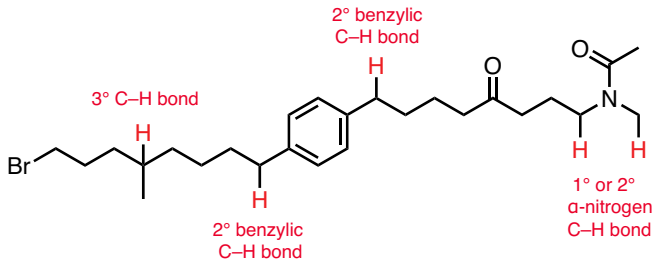


Figure 1. Conventional Functional-Group vs. C–H Functionalization Based Reactivity

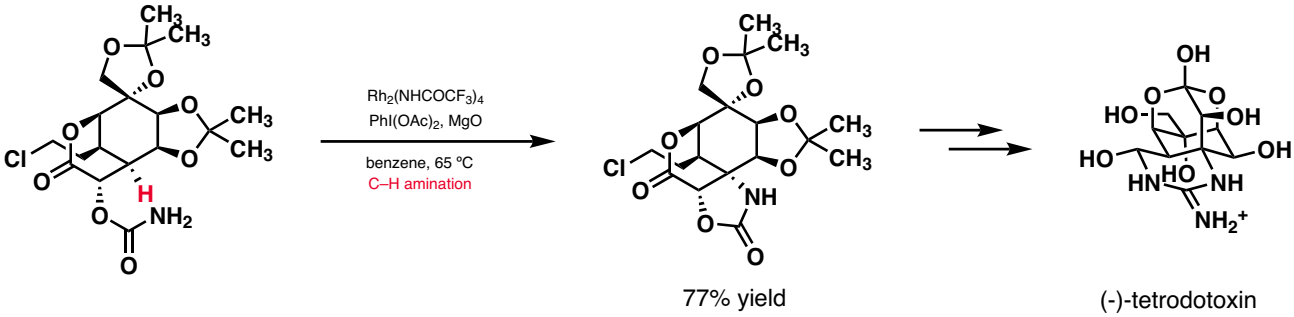


Figure 2. Late-stage C–H Amination in the Total Synthesis of (-)-Tetrodotoxin by Du Bois

Similarly, the synthesis of industrially important compounds has seen huge effects from the recent development of C–H functionalization, particularly in the ability to rapidly generate chemical diversity from a lead compound scaffold. An early example of this application is given by Sawada and coworkers' successful invention of irinotecan, an important chemotherapeutic agent.[5] Two C–H functionalization reactions in close succession, a C–H alkylation followed by a C–H oxidation, allowed the team to access numerous analogues that improved on the starting compound's pharmacological properties, including irinotecan (**Figure 3**).

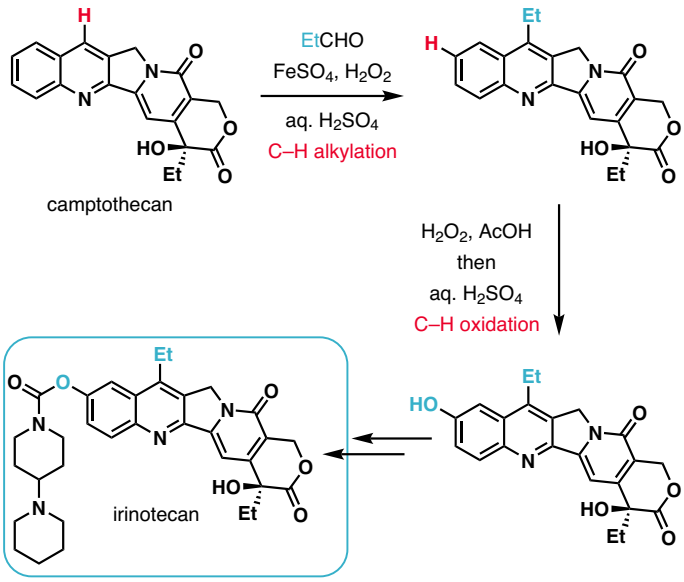


Figure 3. C–H Functionalization in the Synthesis of Chemotherapeutic Agent Irinotecan

While clearly there are manifold advantages to the application of C–H functionalization logic,[6] many curricula for organic chemistry have not yet been updated to reflect this approach. Recognizing this transitional phase, our manual aims to bridge the gap between traditional, functional-group centered synthetic thinking and the opportunities available from C–H functionalization approaches. It is clear that a similar level of familiarity with and understanding of C–H functionalization methods to traditional methods will be required to enable confident and effective use of C–H functionalization in synthetic schemes.

Our manual has 3 main goals:

1. introduce the synthetic community to common C–H functionalization reactions and help facilitate their application in the laboratory
2. use an organizational framework and reactivity discussion to help build an intuition for where and how C–H functionalization reactions might be applied in synthetic schemes
3. inspire further exploration in the rich and versatile field of C–H functionalization

Our manual opens with a curated list of specific C–H functionalization reactions that have found applications in synthetic chemistry schemes. We have provided, when applicable, general tips for performing these reactions as suggested by their developers to aid in successful execution. Significant effort has been put into visualizing these reactions in a manner that helps illustrate the synthetic value of the disconnection. Together with a list of relevant materials at the end, we hope to lower the bar for interested chemists setting up these specific reactions.

To help build intuition around C–H functionalization, we've organized the specific examples into common reaction classes based on several factors: whether the transformation is directed by a coordinating functionality on the substrate (directed vs. undirected), the hybridization of the functionalized C–H bond (sp^2 or sp^3; sp^1 C–H bonds have not been included in this discussion), and whether the process is metal-mediated or radical in character. As many reactions within the same class conform to similar selectivity trends, general rules of thumb for predicting reactivity and selectivity for each class are provided. These rules both enable the application of the reactions presented in this guide and, ideally, many of those not covered, so long as the reaction in question can be classified within one of the provided categories. In this sense, the manual is meant to serve as a reference for practicing synthetic chemists to help develop and supplement their intuition for engaging C–H bonds in selective transformations.

It would be impossible to include all synthetically relevant examples of C–H functionalization in this guide. However, the reactions that have been included were selected, in part, to showcase the power and selectivity of these valuable transformations and give some conception of what sorts of reactions might be possible and, as a result, findable in the literature. New and powerful C–H functionalization reactions continue to be reported at an incredible pace, and interested readers are directed to the thriving literature to expand their toolbox to the maximal extent.

Directed C–H Functionalization

Introduction

A serious challenge for C–H functionalization reactions is distinguishing between many electronically and sterically similar C–H bonds within a molecule. While some of the subtle principles used to achieve selectivity in an undirected, or non-covalent sense, will be discussed later, a simple selectivity principle one could imagine using is covalent attachment of the C–H activating species to the substrate, with the geometry constraints inherent in the resultant intramolecular process limiting the potential C–H bonds to be activated (**Figure 4**).

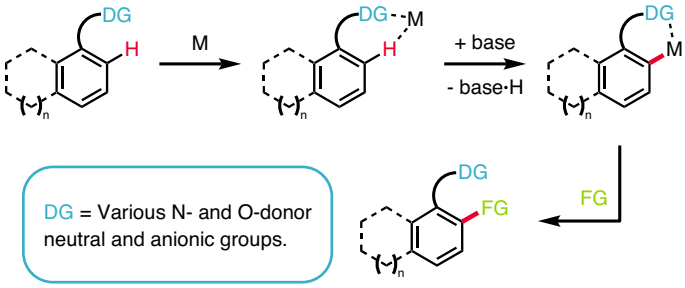


Figure 4. General Strategy for Directed C–H Functionalization

This temporary covalency is typically achieved by virtue of catalyst systems containing Lewis acidic metal centers that can be reversibly coordinated by Lewis basic functionalities on a substrate. A list of common coordinating functionalities, or directing groups, is provided in the following section along with some commentary on what metals and sites are often activated using them.

Even with the use of a directing group, in some situations, several distinct C–H bonds might be geometrically accessible by the directed catalyst. Toward understanding how these bonds might be distinguished between, we will review several examples of these competitive situations and derive from them some selectivity principles for directed reactions in general. These principles are unique to whether the reaction proceeds via an organometallic or non-organometallic mechanism, and we will treat each of these situations separately.

Directed Organometallic Principles

Here we define organometallic C–H functionalization as a process whereby a direct metal–carbon bond is formed between the functionalized site and a metal reagent or catalyst during the course of the reaction. Directed reactions involving organometallic processes often achieve selectivity through the enforced proximity of the C–H bond to be activated and the catalyst or reactive species that will cleave the bond. Importantly, the C–H bond must be geometrically accessible to the activating species (**Figure 5**).

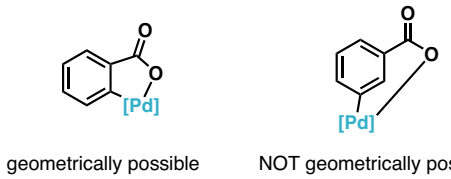


Figure 5. Directed Organometallic C–H Functionalization Selectivity

While the topology of the putative transition state for each specific case should be considered using conformational analysis, several general truisms arise from directed, late metal C–H activation reactions **(Figure 6)**. Firstly, the sites that are functionalized are typically those that would result from a 5- or 6-membered cyclometallated intermediate. If both are available, 5-member metallacycle activations are typically favored.[7]

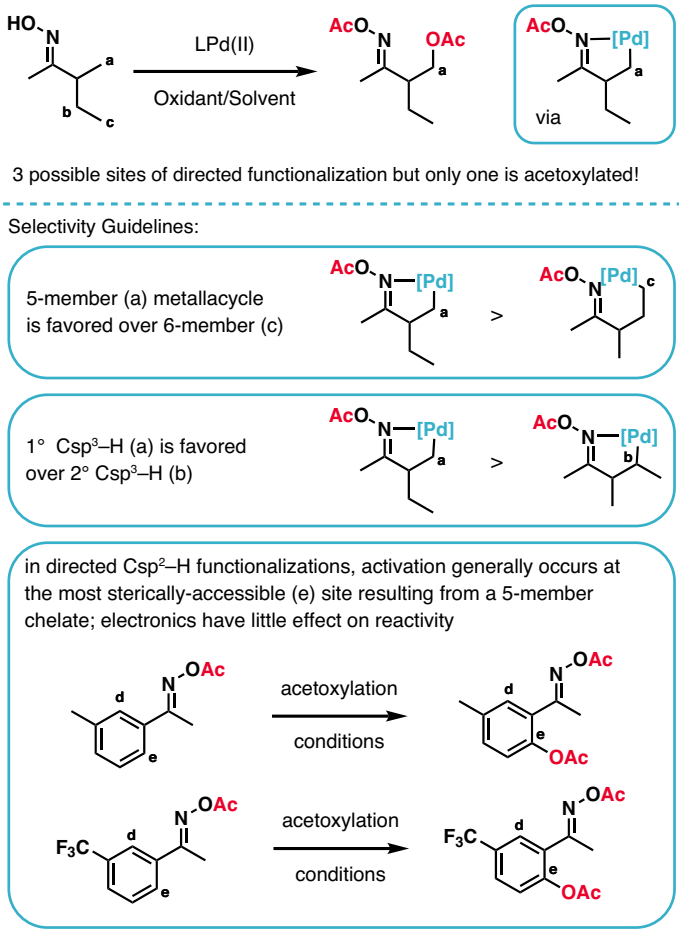


Figure 6. Directed Organometallic C–H Functionalization Selectivity Demonstrated with Acetoxylation[1]

Common Conditions

Solvent:	1:1 $AcOH/Ac_2O$ (0.12M)
Oxidant:	$PhI(OAc)_2$
Pd Source:	$Pd(OAc)_2$ (5 mol %)
Temperature:	80 °C

For sp^3 activations, if given an otherwise equal choice, late metal C–H activation (e.g., those of noble metals) will often prefer to engage 1° C–H bonds over 2° or 3°, presumably due to the partial carbanionic character of the transition state and resultant alkyl intermediate, though steric effects may also contribute to this selectivity.

For sp^2 activations, sterics, and to a much lesser extent electronics, play an important role in selectivity. While several mechanisms are possible for metalating sp^2 sites, each with distinct selectivity, many recently developed directed catalytic techniques rely on a concerted metalation-deprotonation (CMD) process.[8] Experiments have shown sterics to be the predominant factor in the selection of directed CMD-type activation processes, with the most sterically accessible C–H bond being preferred for functionalization. Numerous studies have also shown these reactions to be quite insensitive to electronic effects,[9] with this indifference being one of the key means of distinguishing between CMD and the electronically controlled electrophilic aromatic substitution (EAS). With this said, several CMD reactions have shown a slight preference for electron-deficient C–H bonds in intramolecular competition experiments,[9a] suggesting that some selectivity might be achieved if a synthesis calls for such situations.

However, it is important to note that the site selectivity of these reactions can sometimes be modified by the inclusion of certain key additives. Notably, the inclusion of norbornene (or norbornene derivative) in palladium-catalyzed alkylation allows for the selective functionalization of the C–H bond *meta* to the directing element of an arene, a position which is geometrically inaccessible when using most directing groups (**Figure 7**).[10] This change in reactivity is due to a Catellani-like reversible functionalization with norbornene at the original *ortho* position to scaffold a second C–H functionalization at the previously *meta* now-*ortho* position of the arene. While rare, these sorts of selectivity-modifying conditions can be quite useful and should be considered when atypical positions are being targeted with directed C–H functionalization.

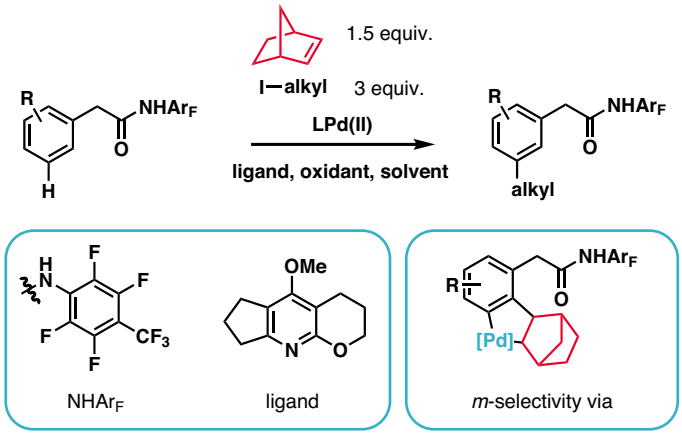


Figure 7. Achieving *meta*-Selective C–H Functionalization of Arenes with a Transient Mediator

Common Conditions

Solvent:	DCE
Ligand:	(20 mol %)
Oxidant:	AgOAc
Pd Source:	$Pd(OAc)_2$ (10 mol %)
Temperature:	95 °C

Hints and Tips

DCE is being heated above its boiling point, ensure that adequate precautions for sealed, pressurized reactions are taken.

Many noble-metal carboxylate catalysts are believed to activate C–H bonds via CMD, so be particularly mindful of the above selectivity guidelines if the reaction conditions contain a late transition metal (Pd, Ru, Co, etc.) and a carboxylate or carbonate ligand, additive, or base (e.g., KOAc, Cs_2CO_3).

Conversely, late, heavy metal activations (e.g., Hg and Pt) are often believed to proceed through electrophilic aromatic substitution, meaning that their selectivity should be analogous to that of the Friedel–Crafts reaction.[8]

Directed Reactions (Non-Organometallic Activation)

Some catalysts that achieve C–H activation through non-organometallic mechanisms (e.g., hydrogen atom abstraction) have shown the capacity to be directed by functional groups on certain substrates. A representative example is the performance of Fe(PDP) on substrates containing a carboxylate functionality, wherein profound selectivity in the ultimate lactonization can be achieved, presumably through coordination of the carboxylate to the iron center (**Figure 8**).[11]

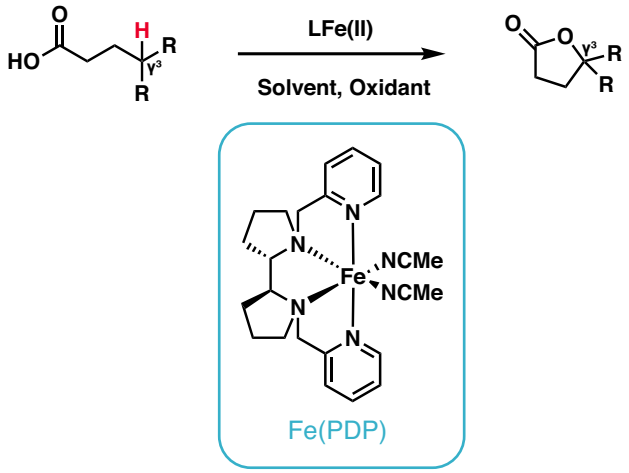


Figure 8. Example of Directed Non-Organometallic C–H Functionalization

Common Conditions

Solvent:	MeCN (concentration changes with each addition)
Oxidant:	H_2O_2 (3 x 1.2 equiv.)
Fe Source:	Fe(PDP) (3 x 5 mol %)
Temperature:	23 °C

Hints and Tips

Three iterative additions of Fe(PDP) and H_2O_2 are made at 0, 10, and 20 minutes.

An important reason for distinguishing between organometallic and non-organometallic mechanisms is the vastly different preferences inherent to these reaction classes within the directed molecule. For example, these Fe(PDP) reactions are believed to proceed via a hydrogen atom abstraction-radical rebound mechanism, whose selectivity follows the rules of hydrogen atom transfer/abstraction (see Undirected Sp^3: Radical-Based Methods (PCET/HAT)). This mechanism informs the user that 2° and 3° C–H bonds will be highly reactive for sp^3 activations using this system, which stands in stark contrast to organometallic mechanisms wherein 1° will be favored over 2° and 3° options.

Directed, non-organometallic C–H functionalization reactions have yet to achieve the level of sophistication of their late metal, organometallic relatives; however, be sure to consider the potential for such processes to be directed when designing reaction routes.

Directing Group Series

C–H functionalization retrosynthetic schemes, much like traditional functional-group strategies, must take a holistic view of potential reactivity at each proposed step, with chemoselectivity no less a concern for these methods than others. In particular, it is often the case that more than one potential directing element may be present in a desired C–H functionalization substrate. Fortuitously, in the same way that it is possible to distinguish a carboxylic acid from an ester when performing a reduction on the basis of reactivity, achieving selectivity between competing directed groups can be achieved through the appropriate selection of metals, ligands, additives, and solvents. The effects that can be realized through these variations are far too numerous and subtle to treat exhaustively; however, careful study has resulted in some useful trends that, while not always extensible to related systems, are a useful starting point for considering reactivity.

Pd(II) Carbonyl and Sulfonyl-Based Directing Groups

A series of directing group ability has been assembled through intramolecular competition studies for the *ortho*-chlorination of arenes, providing a tentative ordering for palladium carboxylate-catalyzed, functional group-directed C–H functionalization (**Figure 9**).[12]

Much work has been performed on these sorts of native directing groups, many of them classified as 'weak coordinators,'[13] with careful studies showing that their reactivity can exceed that of 'stronger' directing elements, such as *N*-containing heterocycles.[14]

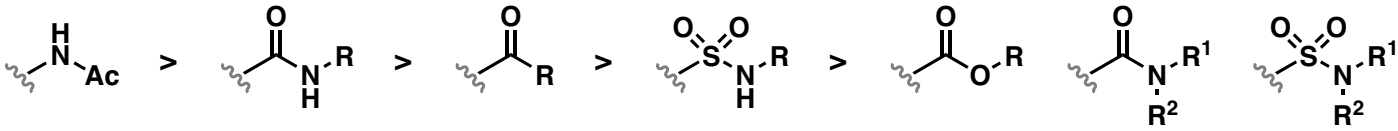


Figure 9. Reactivity Trend for Pd(II) Carbonyl-based Directing Groups

Ru(II) Carbonyl-based Directing Groups

The development of analogous series for other metals remains an ongoing area of study. Preliminary work with ruthenium[15] performing C–H hydroxylations has provided the series shown in **Figure 10**.

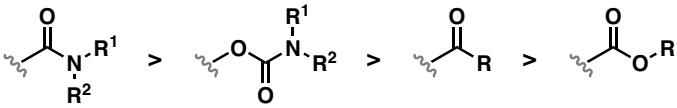


Figure 10. Reactivity Trend for Ru(II) Carbonyl-based Directing Groups

N-Containing Heterocycles

Lewis basic heterocycles such as pyridines, quinolines, oxazoles, pyrimidines, and many others can also function as directing groups for organometallic C–H functionalization.[16] Be mindful of the presence of Lewis-basic nitrogens in C–H functionalization substrates, their potential to enable directed C–H functionalization and, importantly, their potential to outcompete 'weaker' directing groups such as carboxylate, amide, and ketone.

Effect of Catalyst Identity

The application of directing group series comes with the caveat that ancillary ligands can have a profound effect on the ability of a given metal to both coordinate to a directing group and to perform C–H activation. Countless examples in the palladium C–H functionalization literature have shown the presence of a reaction-specific exogenous ligand to be essential for product formation, with changes in directing group often necessitating redesign of the complimentary ligand.[17] Furthermore, change of functionalization reaction, from hydroxylation to arylation to vinylation, can also require a new ligand framework for success.

This effect is certainly not unique to palladium. An illustrative example from Murai and coworkers,[18] has shown two complexes of ruthenium to have orthogonal selectivity in a directed hydroarylation reaction, with each complex responding to a different directing element (**Figure 11**).

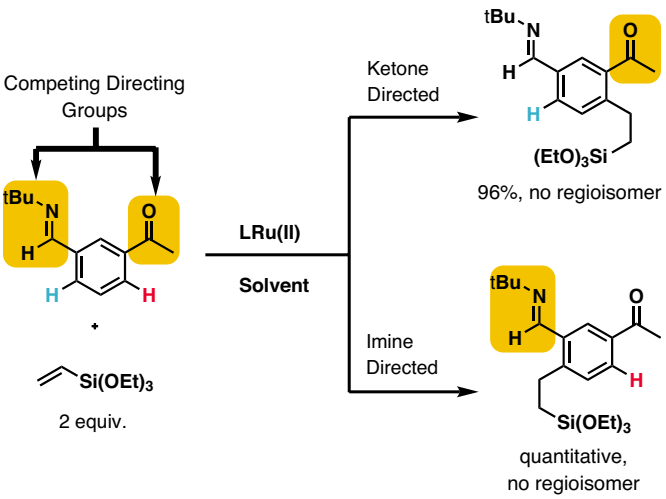


Figure 11. Orthogonal Selectivity with Competing Directing Groups

Ketone-Directed Ruthenium Alkylation Conditions:

Solvent:	toluene
Reagent:	vinyl silane (2. equiv.)
Ru Source:	$Ru(H)_2(CO)(PPh_3)_3$ (2 mol %)
Temperature:	135 °C
Time:	3–5 h

Imine-Directed Ruthenium Alkylation Conditions:

Solvent:	toluene
Reagent:	vinyl silane (2. equiv.)
Ru Source:	$Ru_3(CO)_{12}$ (2 mol %)
Temperature:	135 °C
Time:	3–5 h

These examples illustrate that extrapolation from trends in directing group ability, while useful, is inherently limited by the complex interdependence of directing group and catalyst identities. Luckily, the strong influence of each of these variables permits wide exploration of reaction conditions for a desired C–H functionalization transformation, giving a reasonable probability of finding a successful reaction given sufficient screening.

Native Directing Elements

Since the directing element of a molecule must be stable to the C–H functionalization conditions to be applied, C–H oxidation-prone functional groups such as free amines and alcohols are seldom used as directing elements. However, some otherwise common functional groups work quite well to guide the action of C–H functionalization catalysts.

For the purposes of illustration, several examples of 'native' functional-group-directed C–H functionalization are provided below, each using a different metal and installing a different functional group. The library of known reactions is vast, and the interested chemist is encouraged to explore the literature to find related reactions that may be of use to their specific synthetic needs.

Carboxylic Acid-Directed Palladium Arylation:[19]

The ubiquity of acetate as an X-type ligand in C–H functionalization catalysts makes it unsurprising that carboxylates are able to coordinate these complexes and direct the activation step. The palladium-catalyzed example in **Figure 12** relies on the exchange of a potassium carboxylate into the inner sphere of the palladium catalyst, permitting the oxidative coupling of aryl trifluoroboronates and benzoic acids.

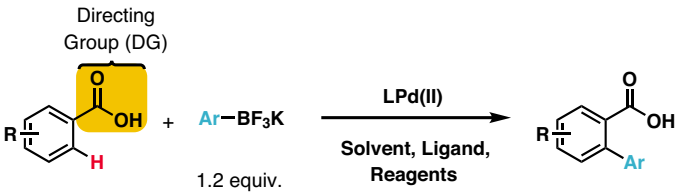


Figure 12. Carboxylic Acid-Directed Palladium Arylation

Common Conditions

Solvent:	*t*-BuOH (0.33 M)
Ligand:	1,4-benzoquinone (50 mol %)
Reagents:	K_2HPO_4; O_2 or air
Pd Source:	$Pd(OAc)_2$ (10 mol %)
Temperature:	100 °C
Time:	24 h

Hints and Tips

Caution should be taken when handling pressurized oxygen.

Amide-Directed Rhodium Annulation:[20]

One application of C–H functionalization that has found widespread use is the assembly of heterocycles through directed alkylation/annulation reactions. The rhodium-catalyzed example in **Figure 13** allows for the rapid synthesis of isoquinolones from simple benzoic amides and alkynes through an amide-directed C–H alkylation followed by reductive elimination.

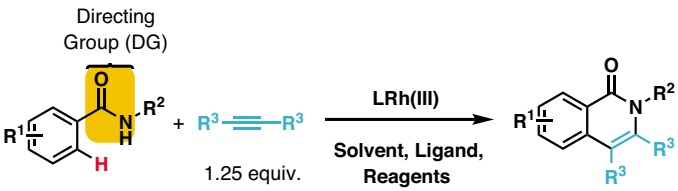


Figure 13. Amide-Directed Rhodium Annulation

Common Conditions

Solvent:	*t*-amyl alcohol (0.14 M)
Reagents:	alkyne (1.25 equiv.)
Rh Source:	$[Cp^*RhCl_2]_2$ (2.5 mol %)
Cu Source:	$Cu(OAc)_2 \bullet H_2O$ (2.1 equiv.)
Temperature:	110 °C
Time:	16 h

Ketone-Directed Ruthenium Imidation:[21]

Ketones, while less developed than amides and carboxylates as directing groups, are nonetheless able to direct C–H functionalization reactions, especially of ruthenium. The example in **Figure 14** uses the readily available $[(p\text{-cymene})RuCl_2]$ to imidate benzyl ketones at the *ortho* position using tosyl hydroximides.

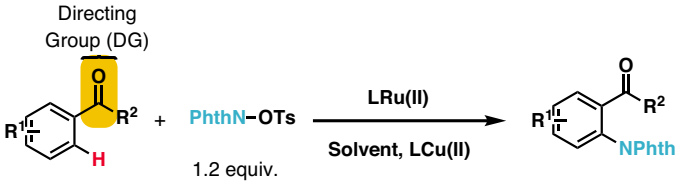


Figure 14. Ketone-Directed Ruthenium Imidation

Common Conditions

Solvent:	1,4-dioxane (0.25 M)
Rh Source:	$[(p\text{-cymene})RuCl_2]$ (5 mol %)
Cu Source:	$Cu(OAc)_2 \bullet H_2O$ (50 mol %)
Temperature:	110 °C
Time:	24 h

Installed Directing Groups

In cases where the native functional groups of a substrate are not able to direct a C–H functionalization event and/or are unstable to the functionalization conditions, it has been found that covalent modification with an auxiliary group can improve reactivity markedly. Many such auxiliaries have been developed for this purpose and a small subset of these is provided below.

8-Aminoquinoline and Perfluorotoluamide

Native carboxylic acids and amides, while capable of driving some C–H functionalization reactions (see above), provide insufficient reactivity for many protocols. Toward increasing the directing ability of this functional group class, it has been found that forming amides with either 8-aminoquinoline (benzoic acids) or 4-aminoperfluorotoluene (aryl acetic acids) is often successful.

The 8-aminoquinolinamide directing element has been successfully applied for C–H activation reactions using a variety of metals, including palladium, copper, iron, cobalt, and nickel.[22] The directing element can be assembled through amide coupling methods to join 8-amino-quinoline with a suitably activated carboxylic acid equivalent (**Figure 15**).[23] Auxiliary removal can be achieved through saponification (**Figure 17**).[24]

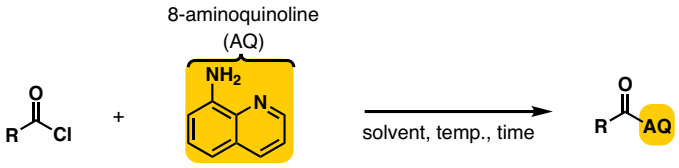


Figure 15. 8-Aminoquinoline Directing Group Installation

Common Conditions

Solvent:	CH_2Cl_2 (0.66 M)
8-Aminoquinoline:	1.0 equiv.
Acid Chloride:	1.5 equiv.
Temperature:	23 °C
Time:	6 h

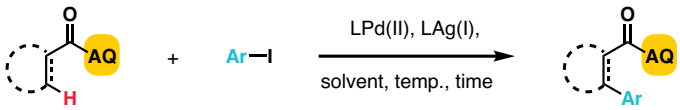


Figure 16. 8-Aminoquinoline as Directing Group in C–H Arylation

Common Conditions

Solvent:	neat, under air atmosphere
Aryl Iodide:	4.0 equiv.
Pd(II) Source:	$Pd(OAc)_2$ (5 mol %)
Ag(I) Source:	AgOAc (1.1 equiv.)
Temperature:	110 °C
Time:	5 min–5 h

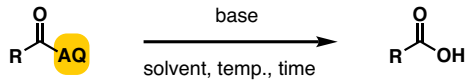


Figure 17. 8-Aminoquinoline Directing Group Removal

Common Conditions

Solvent:	ethanol
Base:	NaOH (15 equiv.)
Temperature:	130 °C
Time:	72 h

The perfluorotoluamide directing group has found wide application in palladium-mediated sp^2 and sp^3 C–H functionalization.[25] The auxiliary is typically assembled through amide coupling of an activated carboxylic acid and the commercially available 4-aminoperfoluorotoluene (**Figure 18**). Once the directing group is no longer needed, the free carboxylic acid can be regenerated through acidic hydrolysis (**Figure 20**).

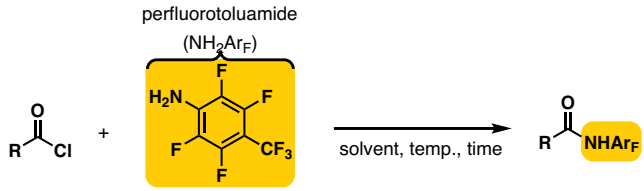


Figure 18. Perfluorotoluamide Directing Group Installation

Common Conditions

Solvent:	toluene (0.2 M)
4-aminoperfluorotoluamide:	1 equiv.
Acid Chloride:	1.1 equiv.
Temperature:	reflux
Time:	12 h

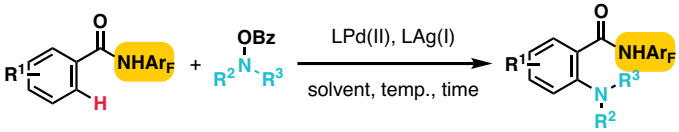


Figure 19. Perfluorotoluamide as Directing Group for C–H Amination

Common Conditions

Solvent:	DCE (0.2 M)
Pd(II) Source:	$Pd(OAc)_2$ (10 mol %)
Ag(I) Source:	AgOAc (1.0 equiv.)
O-benylhydroxylamine	1.0 equiv.
CsF:	2.0 equiv.
Temperature:	130 °C (sealed tube)
Time:	18 h

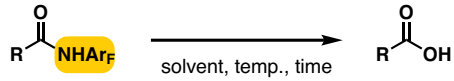


Figure 20. Perfluorotoluamide Directing Group Removal

Common Conditions

Solvent:	2:1 TFA/HCl (0.03 M)
Temperature:	100 °C
Time:	12 h

2-Picolinamide

While free amines are typically poorly behaved for directed C–H functionalization, their masking as 2-picolinamide directing groups has enabled a variety of sp^2 and sp^3 functionalizations to be performed using palladium.[22, 26] Installation of the auxiliary is achieved via standard amide coupling methods and removal is through basic hydrolysis (**Figures 21–23**).[27]

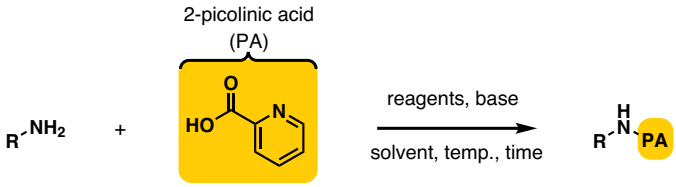


Figure 21. 2-Picolinamide Directing Group Installation

Common Conditions

Solvent:	CH_2Cl_2 (0.8 M)
Reagents and base:	picolinic acid (1.1 equiv.), HOBT (1.1 equiv.); then DIPEA (2.2 equiv.), EDC (1.1 equiv.); then amine (1.0 equiv.)
Temperature:	0 °C, warm to r.t. overnight
Time:	16 h

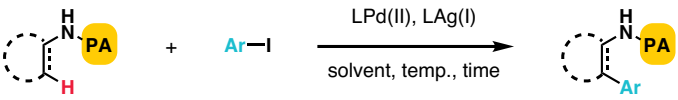


Figure 22. 2-Picolinamide as Directing Group for C–H Arylation

Common Conditions

Solvent:	CH_2Cl_2 (0.8 M)
Reagents and base:	picolinic acid (1.1 equiv.), HOBT (1.1 equiv.); then DIPEA (2.2 equiv.), EDC (1.1 equiv.); then amine (1.0 equiv.)
Temperature:	0 °C, warm to r.t. overnight
Time:	16 h

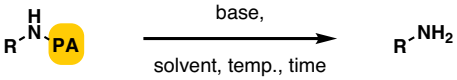


Figure 23. 2-Picolinamide Directing Group Removal

Common Conditions

Solvent:	2:1:1 MeOH/THF/H_2O (0.07 M)
Base:	NaOH (1.5 equiv., 1N solution)
Temperature:	reflux
Time:	3.5 h

Oximes and Oxime Ethers

When the weakly coordinating ketone functional group is unable to direct palladium-catalyzed C–H functionalization reactions it has been found that conversion to the strongly coordinating O-carboxy oxime[28] or oxime ether[29] can provide reactivity. In the case of acetoxylation reactions, it has been found that a free oxime will be in situ acylated to the acetoxy oxime group.[28] A number of protocols have been developed to convert ketones to oximes and their derivatives, typically condensing the parent hydroxyl- or alkoxylamine with the starting ketone (**Figure 24**). Following this, removal is typically achieved through hydrolysis which may or may not be preceded by reductive cleavage of the N–O bond.[28]

Figure 24. Oxime Directing Group Installation

Common Conditions

Solvent:	pyridine (0.35 M)
Reagents:	NH_2OH • HCl (1.35 equiv.)
Temperature:	80 °C
Time:	15 min

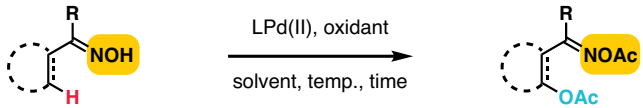


Figure 25. Oxime Directing Group for C–H Acetoxylation

Common Conditions

Solvent:	1:1 AcOH/Ac2O (0.12M)
Pd(II) Source:	$Pd(OAc)_2$ (5 mol %)
Oxidant:	$PhI(OAc)_2$ (2 equiv.)
Temperature:	100 °C
Time:	12 h

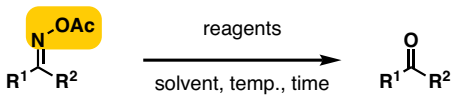


Figure 26. Oxime Directing Group Removal

Common Conditions

Solvent:	MeOH (0.46 M) then equal volume H_2O
Reagents:	0.45 equiv. K_2CO_3 then 3.5 equiv. $NaHSO_3$
Temperature:	80 °C
Time:	6 h

Undirected, Metal-Mediated C–H Functionalization

Undirected Sp^2: Borylation

Cross coupling methods have become one of the premier reaction classes for the predictable and efficient assembly of new chemical bonds.[30] Among the most popular coupling partners in these schemes are carbon-boron species, with these reagents being used in reactions as diverse as the Suzuki-Miyaura coupling and recent photoredox-enabled nickel protocols.[31] While these reactions are highly enabling, it becomes clear that they are inherently limited by the availability of boron coupling partners. Iridium-catalyzed C–H borylation to rapidly and predictably install boronic esters has thus become an essential tool in the playbook of synthetic chemists (**Figure 27**).[32]

The direct iridium-catalyzed borylation of aromatic rings is generally controlled by steric effects, where functionalization next to a non-hydrogen substituent is highly disfavored. Electronic effects are typically overshadowed by steric contributions for substituted benzenes.[32]

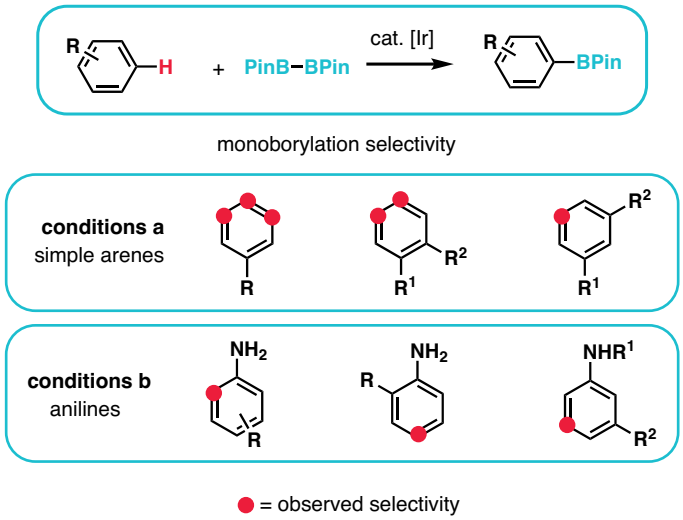


Figure 27. Selectivity in Ir-Catalyzed C–H Borylation

Conditions A[32]

Solvent:	neat, reaction prepared in glovebox
Ir Source:	1.5 mol% 0.5[IrCl(COD)]$_2$, 3 mol% bpy
Reagents:	1.0 equiv. B_2Pin_2, 60 equiv. arene
Temperature:	80 °C
Time:	16 h

Conditions B[33]

Solvent:	THF (1.0 M), prepared in glovebox, HBPin added in two 1.5 equiv. portions
Ir Source:	0.25 mol% 0.5[IrCl(COD)]$_2$, 1 mol% Me_4Phen
Reagents:	2 x 1.5 equiv. HBPin, 1 equiv. aniline
Temperature:	80 °C
Time:	16 h

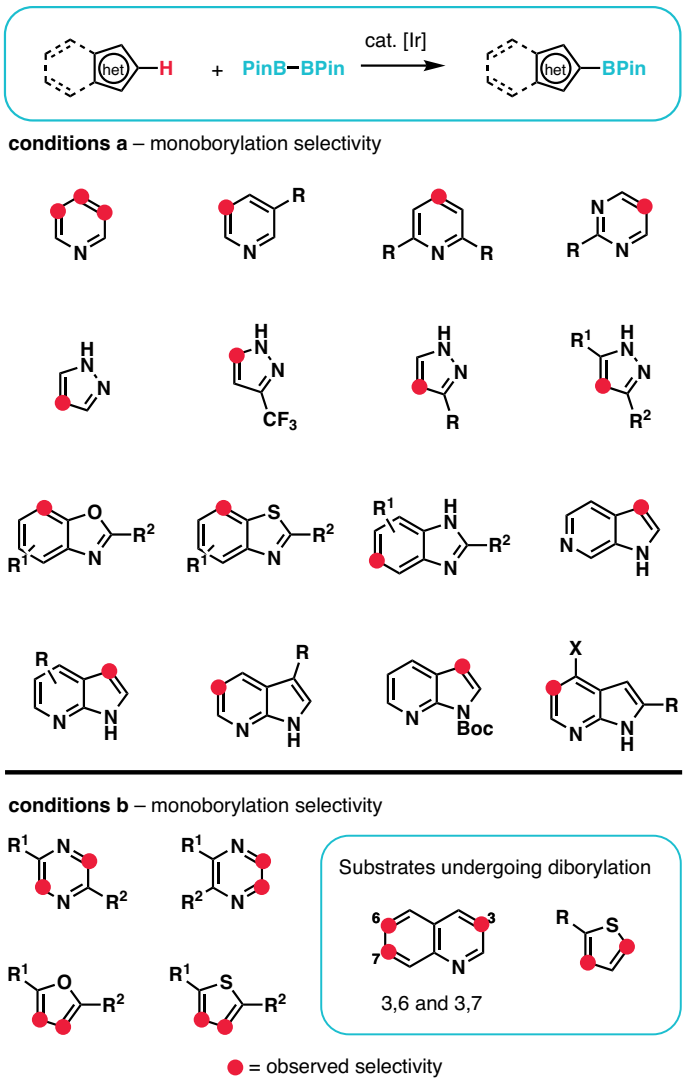


Figure 28. Selectivity in Ir-Catalyzed C–H Borylation of Heteroarenes

Conditions A[34]

Solvent:	THF (0.5 M), reaction prepared in glovebox
Ir Source:	0.25–2.5 mol% 0.5[Ir(COD)OMe]$_2$, 0.5–5.0 mol% Me_4Phen
Reagents:	1.0–1.5 equiv. B_2Pin_2,
Temperature:	80 °C
Time:	4–48 h

Conditions B[35]

Solvent:	MTBE (0.4 M), Prepared in glovebox, Heated in a microwave reactor
Ir Source:	3 mol% 0.5[Ir(COD)OMe]$_2$, 3 mol% dtbbpy
Reagents:	1.0 equiv. B_2Pin_2,
Temperature:	80 °C (Microwave irradiation)
Time:	5–60 min

For monosubstituted benzene rings typically *meta* and *para* borylated products are formed, with a statistical bias for the *meta* product.

1,3-Disubstituted benzenes typically exhibit exquisite selectivity for 5-borylation, allowing for the highly predictable installation of boron into highly functional building blocks.[32] An interesting exception to this reactivity occurs with free anilines,[33] where borylation at the position *ortho* to the NH_2 group is the major reaction outcome, unless the aniline is already *ortho*-substituted. However, this directing effect is lost once the aniline becomes secondary, with traditional selectivity again being observed.

Heteroarenes can also be efficiently borylated using modifications of the original borylation procedure,[34,35] with observed selectivities shown in **Figure 28**.

While plentiful, the list of heteroaromatic motifs above is certainly not exhaustive. Toward predicting selectivity for non-represented heteroarenes, it has been found that heteroaromatics have some additional selectivity rules when compared to simple arene substrates.[34] These can add to and, in some cases, override the a priori predicted steric preferences of the substrate, necessitating their inclusion in C–B disconnection strategies. Most significantly:

1. Borylation will not occur next to (alpha to) a ring nitrogen with either a free lone pair (e.g., pyridine) or N–H bond (e.g., pyrrole).[33] Similarly, borylation will not occur adjacent to ring nitrogens protected with a Boc group.[36]

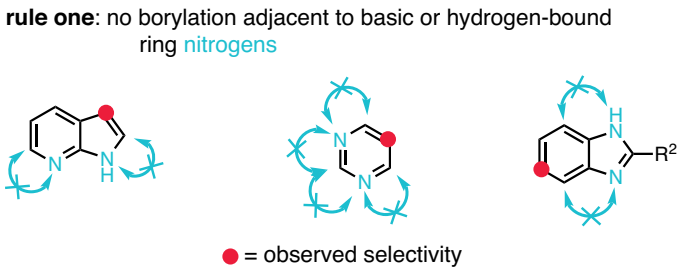


Figure 29. Selectivity Rules for C–H Borylation of Heteroarenes

2. If comparing otherwise accessible sites, borylation will occur preferentially adjacent to ring oxygen or sulfur atoms.

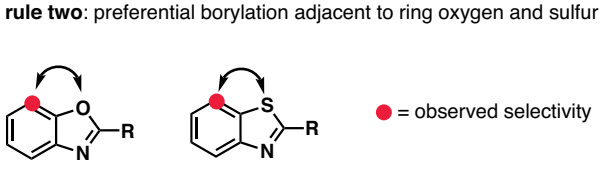


Figure 30. Selectivity Rules for C–H Borylation of Heteroarenes

Undirected Sp^2: Direct Arylation

While directing functionality was shown to be highly effective for permitting regioselective metalation and subsequent functionalization of C–H bonds using late-metal carboxylate catalysts, it is known that C–H functionalizations of aromatic species in the absence of a directing group are also possible.[37] These so-called "direct arylation" reactions of simple arenes have not yet reached the level of sophistication of their functional-group-directed counterparts, with many protocols requiring long reaction times, exotic catalysts, and the presence of the arene substrate in solvent quantities. Heteroaromatics, however, have been shown to be amenable to selective C–C bond formation using aryl bromides and palladium catalysis. A subset of heterocycles known to undergo selective arylation along with their determined regioselectivities are shown in **Figure 31**.[38]

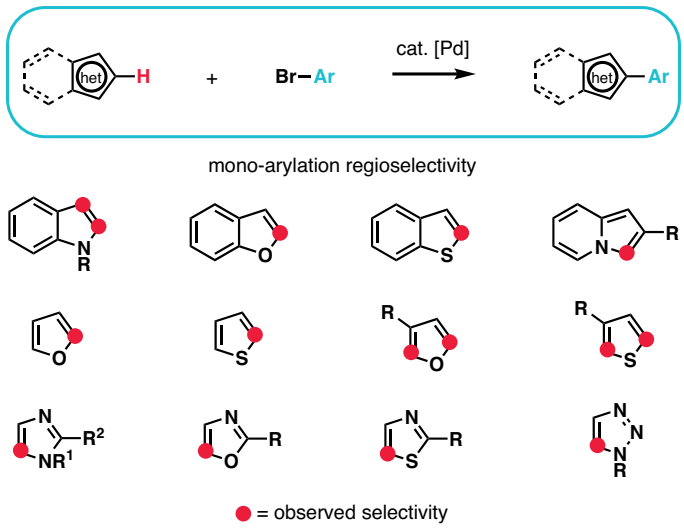


Figure 31. Undirected C–H Arylation of Heteroarenes

Common Conditions

Solvent:	DMA (0.3 M)
Pd(II) Source:	$Pd(OAc)_2$ (2 mol %), PCy_3•HBF_4 (4 mol %), PivOH (30 mol %)
Aryl Bromide:	1.0 equiv.
Base:	K_2CO_3 (1.5 equiv.)
Temperature:	100 °C
Time:	14 h

Further study has found that chloride can be used as a temporary blocking group to improve the selectivity for heteroarenes with otherwise promiscuous reactivity,[38] providing a useful tool for overcoming recalcitrant product ratios.

Undirected Sp^3: C–C Bond Formation

The controlled, metal-mediated insertion of a carbene into a specific C(sp^3)–H bond offers the exciting possibility of rapidly accessing complex and stereochemically rich carbon frameworks from unfunctionalized feedstock chemicals in a straightforward and concise fashion. The challenge, as highlighted throughout this guide, is that of reliably selecting a defined site of reaction from amongst the abundance of C–H bonds in a typical organic molecule.[39] Moving from C(sp^2)–H to C(sp^3)–H bonds demands an extra level of sophistication from the transformation, with the motivating opportunity to access chiral products.

Carbene C–H Insertion Mechanism

Early studies in this field revolved around the use of copper catalysts, albeit with limited synthetic success.[40] Toward improving this, the ability of many late transition metals to mediate carbene C–H insertion has also been assessed. While complexes of Ru, Pt, Ir, Ni and Cu have all been shown as capable catalysts,[41] the use of rhodium complexes has come to dominate the field, particularly the dirhodium(II) tetra-carboxylate and -carboxamidate complexes. These frameworks are particularly successful both for their ability to stabilize the reactive carbene center and the modular nature of the ligand structure, key features in influencing site- and stereo-selection.[42] These complexes are also convenient in practical terms, being air and moisture stable solids that require no special handling and can be stored indefinitely. The reactive intermediate carbenes can also be readily generated in situ from diazo compounds, though there has been much recent work exploring alternative carbene precursors, such as triazoles.

The generally accepted catalytic cycle is shown in **Figure 32**: formation of the metal-stabilized carbene through complexation of the diazo compound with the active metal site and extrusion of nitrogen gas followed by C–H insertion with concomitant C–C bond formation.

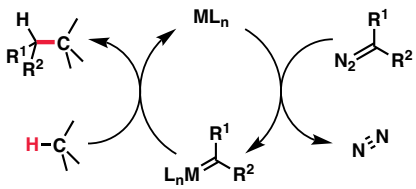


Figure 32. Carbene C–H Insertion Mechanism

The specifics of the key C–H insertion event of dirhodium catalyzed carbene chemistry has been the subject of significant investigation. Recent theoretical calculations describe an event that begins with considerable hydride transfer character, with a C–H–C bond angle in the range of 117–165°,[43] suggesting that the C–H bond of the substrate approaches the metal bound carbene carbon at a vector nearly orthogonal to the rhodium carbene plane (**Figure 33**).

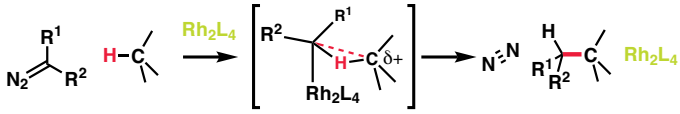


Figure 33. Carbene C–H Insertion

Predicting Reactivity and Selectivity in Carbene C–H Insertions

Selectivity in dirhodium catalyzed carbene C–H insertion is determined by considering a balance of the stereo-electronics of the substrate, the reactivity of the carbene, the electrophilicity of the rhodium carbene intermediate and the steric environment surrounding the reactive metal center (**Figure 34**). In the sections below a brief description of the factors that influence each of these considerations is outlined.

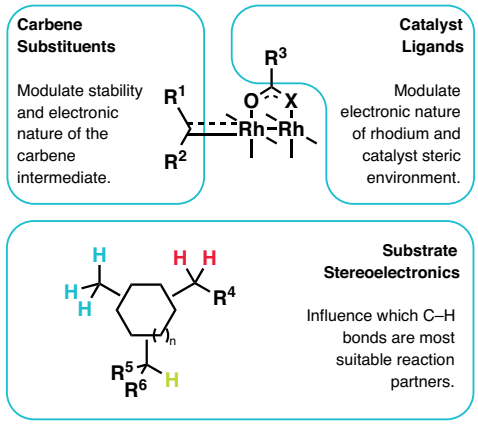


Figure 34. vFactors Affecting Dirhodium Catalyzed Carbene C–H Insertions

Carbene Substituents

The stability, and hence reactivity, of a carbene is strongly influenced by the electron-donating (or withdrawing) capacity of the substituents attached to the carbene center. The importance of these effects has led to carbenes used in C–H functionalization being classified by the substituents appending the carbene carbon (**Figure 35**).

Figure 35. Classification of Carbenes by Substituent Type

The acceptor/acceptor and acceptor-only carbenes are highly reactive species. This can be understood by the acceptor groups increasing the electrophilicity of the carbene. Indeed, the reactivity of these species is such that they have almost exclusively been applied in intramolecular C–H insertion reactions. Conversely, the donor group in the donor/acceptor carbenes has a stabilizing effect, reducing the overall electrophilicity (and reactivity) of the carbene, but consequently increasing the lifetime of this intermediate and the selectivity of the reaction.[44] The increased selectivity imparted by the longer-lived intermediate has enabled the application of this class of carbenes in intermolecular C–H insertion reactions. Donor-only carbenes are rare in the literature, largely due to the hazards associated with the generation of the corresponding diazo precursors. However, donor-carbenes generated through alternative species have been shown to undergo intramolecular C–H insertion.[45]

Catalyst Ligands

The ligands that surround the active metal core have a critical influence on the reaction coordinate, both in terms of electronic and steric effects. Tuning the electronic nature of the ligands has a direct impact on the electrophilicity of the metal carbene intermediate. Increasing the electron-withdrawing nature of the ligand increases the electrophilicity of the carbene, effecting an increase in reactivity and associated decrease in selectivity.[42,46] Conversely, surrounding the dirhodium core with less electron-withdrawing ligands decreases the reactivity of the system, typically with a concomitant increase in selectivity.

The primary element that influences chiral induction of these transformations is the stereochemical and spatial configuration of the ligands surrounding the active metal center. It is in this regard that the structure of the dirhodium(II)-paddlewheel complexes becomes highly enabling. By virtue of surrounding the active metal center with 4 chiral ligands, the complex (as a whole) undergoes a process of stereochemical amplification, meaning that a high level of asymmetric induction can be achieved for tetraligated rhodium catalyst even if each ligand has only modest asymmetry. This effect is thought to arise through conformational preferences of the ligands, where smallest group attached to the chiral ligand center is presumed to occupy the small pocket between the ligands in the complex, with the medium and larger groups oriented either above or below the plane of the paddlewheel complex. Thus, 4 different symmetries are possible and sophisticated design of ligands can lead to the synthesis of complexes showing strong symmetry preferences (**Figure 36**).[42,47] The spatial arrangement of these ligands during the C–H insertion step determine the trajectory of the substrate and hence the stereochemical induction. There has been significant investigation into the origins of stereo- and enantio-induction in this transformation and the role that catalyst ligands play in the C–H insertion transition state.[43,48] While an in-depth explanation of how the different ligands classes induce stereochemistry is beyond the scope of this guide, each distinct ligand environment interacts with the incoming substrate in a different way and the majority of ligands are available in both enantiomers. Thus, producing both enantiomeric series for a wide variety of substrates is possible via this method.

Toward extending the possibilities of rhodium catalysts, there has been and continues to be a great deal of effort directed toward the design of ligands frameworks capable of both stabilizing the intermediate metal carbene and directing the stereochemical course of the reaction.[49]

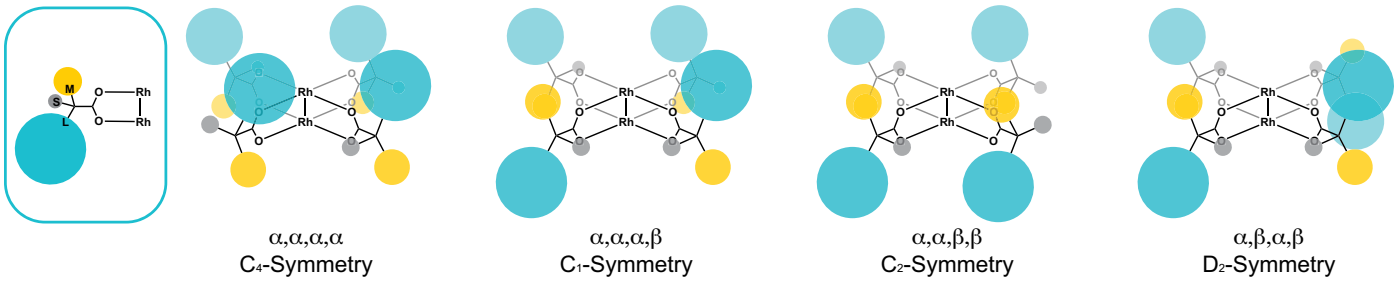


Figure 36. Dirhodium Complex Symmetries

Substrate Stereoelectronics

The reactive nature of a carbene is required to overcome the kinetic barrier to engaging C–H bonds as reaction partners. Given the energetics of these species, it is instructive to consider other common functional groups with which carbenes will competitively or, in some cases, preferentially react when planning a synthetic strategy. Notably, the unshared valence electrons of the carbene are promiscuous and react readily with both Lewis acids and bases and X–H bonds.[50] Unprotected alcohols and amines are thus likely reaction partners, forming the associated O–H and N–H insertion products. Carbenes also react readily with localized and delocalized pi-electron systems, resulting in cyclopropane and cycloaddition adducts. Such is the predilection for carbene cyclopropanation of pi-bonds, that a mono-substituted arene will undergo mono- or bis-cyclopropanation, breaking the aromaticity of the substrate.[51] However, appropriately substituted pi-systems, typically requiring substitution at both the 1- and 4-positions, are unreactive to cycloaddition reactions and can be incorporated into substrates for C–H insertion.

Even with these constraints in mind, there remains a vast scope of chemical space to explore. Comparison of the relative Bond Dissociation Energies (BDE) of competing C–H bonds is a helpful first analysis when determining the likely site of reaction, though it is not the only factor. Consider the fine balance struck between the electronic and steric properties of the substrate (**Figure 37**). From an electronic perspective C–H insertion occurs preferentially at sites most capable of stabilizing the positive charge that builds during the 3-centered transition state. This electronic bias leads to preferential insertion into tertiary over secondary C–H bonds, and secondary over primary C–H bonds. However, as previously alluded to, the ligand framework that surrounds the active dirhodium core can exert a significant steric influence on the transition state, prohibiting insertion at sterically occluded sites. These antagonistic forces allow for remarkable selectivity to be achieved. Sterically large ligand systems prevent insertion at crowded tertiary C–H bonds, and a balance is struck, with the accessible and stabilized secondary C–H bonds emerging as the typical sites for carbene C–H insertion.

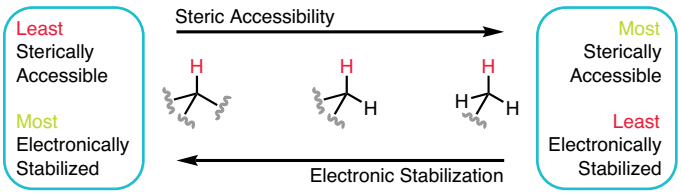


Figure 37. C–H Insertion Selectivity: Sterics and Electronics

Understanding the hydride nature of the C–H insertion event aids in understanding another substrate electronic effect: the impact of activating and deactivating groups. Effective stabilization of a partial positive charge will impart increased reactivity at a particular site, thus promoting insertion into C–H bonds adjacent to electron-donating groups such as alcohols, amines or pi-systems and inhibiting insertion into C–H bonds adjacent to electron-withdrawing groups such as acetates. This electronic effect can also be felt across multiple bonds, exemplified by the beta-oxygen effect, whereby electron deficiency shuts down C–H insertion at this position. A summary of the relative activation of C–H bonds by electron donating substituents is shown in **Figure 38**.

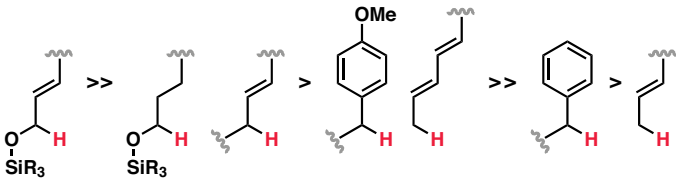


Figure 38. Relative Activation of C–H Bonds by Electron Donating Substituents

Taking a combination of these factors into account, it is possible to understand and predict product outcomes across a range of C–H insertion substrates. An informative study provides a comparative outline of the relative rates of reaction for the dirhodium-catalyzed carbene C–H insertion across a range of small molecule motifs.

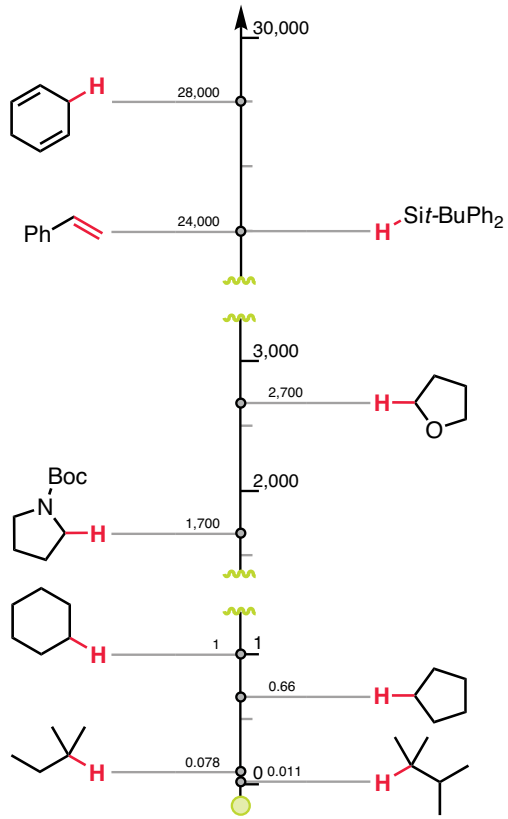


Figure 39. Relative Rates of Carbene Reactivity

Intramolecular Carbene C–H Insertion

Synthetically efficient selective carbene C–H insertion was first demonstrated in an intramolecular scaffold.[41,52,53,54] The increased directing power and control offered by a rigid, geometrically defined orientation, such as that present in an intramolecular configuration, is highly efficient in preferentially forming a single product. Selective reaction is possible even with less stabilized acceptor/acceptor and acceptor-only carbenes in these cases. A survey of the extensive literature published on the intramolecular dirhodium-catalyzed carbene C–H insertion reveals a number of trends that can be employed to reliably predict product formation,[53,54,55] most relevantly that there is a significant preference for 1,5-insertion reactions, forming 5-membered rings. However, this bias can be overcome through the introduction of an activating group with the ability to direct the insertion event to an alternative position, leading to the formation of 4- or 6-membered ring products. When more than one 5-membered ring can be formed the reactivity of the C–H bonds follow the order 3° > 2° >1°. Many examples of carbocycle, lactone and lactam formation are described in the literature.[53,54,55]

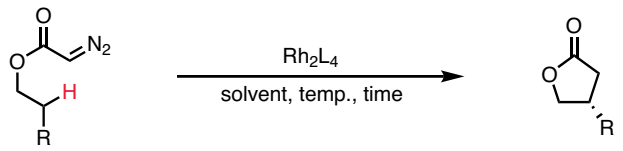


Figure 40. Intramolecular Carbene C–H Insertion

Common Conditions[56]

Solvent:	CH_2Cl_2 (0.02 M—wrt to the catalyst)
Rh(II) Source:	Rh_2(4S-MPPIM)$_4$ (1 mol %)
Diazoacetate:	substrate (2.0 mmol in 2 mL of CH_2Cl_2, (1.0 M), added dropwise over 5 h)
Temperature:	40 °C
Time:	5 h for addition of substrate and then the solvent was evaporated.

Intermolecular Carbene C–H Insertion

Moving from an intra- to an intermolecular reaction manifold not only significantly expands the scope and perspective of this chemistry, but also presents new challenges associated with the selectivity of the process. The removal of the tether-induced preference for a particular ring size means that the number of potentially participating C–H bonds in the substrate expands markedly. Thus, other controlling factors are required in order for a selective transformation to occur. Early studies of the dirhodium-catalyzed intermolecular carbene C–H insertion suffered from low levels of regioselectivity and a multitude of side reactions.[40] However, these studies focused on the use of acceptor/acceptor and acceptor-only carbenes. Subsequent studies in the mid-1990s identified that using donor/acceptor carbenes furnished a more stable carbene intermediate, as mentioned above.[57] This electronic 'push and pull' stabilizes the species to such an extent that it is now capable of selective intermolecular C–H insertion. Even more recently, catalysts have been designed that are capable of stabilizing acceptor-only carbenes to an extent such that they are selective participants in intermolecular C–H insertion reactions.[58]

While having several key differences, much of the knowledge gained from the intramolecular studies can be directly applied to the intermolecular manifold. Removal of the entropic driving force present in the intramolecular scaffold means that the product formation is dependent on subtler stereoelectronic properties. Indeed, activating groups become the primary influence, with the immediate steric surroundings of the C–H bond also playing a significant role. As mentioned before, the balance of electronic and steric factors leads to 2° C–H bonds being the most favored sites for insertion, positioned in the sweet spot of steric accessibility and electronic stabilization. Illustrative examples that highlight the balance that is struck between the steric and electronic properties of a given substrate are shown in **Figure 41**.

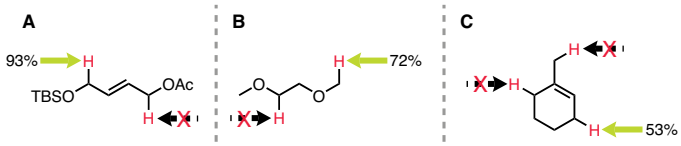


Figure 41. Selectivity for Intermolecular C–H Carbene Insertion

In panel A, the electron-rich nature of the TBS-protected alcohol stabilizes the build-up of positive charge associated with the C–H insertion event, while the electron-withdrawing nature of the acetate protecting group does not, leading to reaction exclusively at one site.[59] In panel B, the impact of electronic factors is highlighted. While it has been established that C–H bonds alpha- to oxygen (or nitrogen) are highly activated to insertion, C–H bonds beta- to oxygen are deactivated. Thus, the inductive effect of oxygen is such that the 2° C–H bonds beta- to oxygen do not undergo insertion reaction, leading to the typically less stabilized primary C–H bond reacting preferentially.[60] The substrate in panel C provides an excellent illustration of the sometimes-subtle steric factors that are in play. This pi-system contains 3 different allylic C–H bond environments: 2 secondary and 1 primary; however, only 1 site is functionalized. This selectivity arises since the reactivity of a 2° C–H bond is considerably diminished if the site adjacent to it is 3°. Even though there are 2 allylic methylene groups in this molecule, the neighboring alkyl substituent hinders reaction on the adjacent methylene carbon.[61]

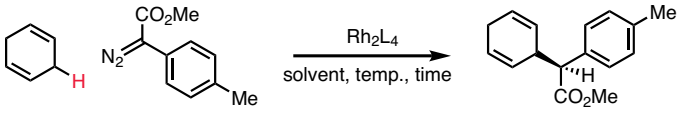


Figure 42. Intermolecular Carbene C–H Insertion

Common Conditions[62,63]

Solvent:	CH_2Cl_2 (0.6 M)
Rh(II) Source:	Rh_2(S-DOSP)$_4$ (1 mol %)
Diazoacetate:	aryldiazoacetate (0.5 equiv.; added dropwise over 3 h as a solution in CH_2Cl_2 (0.08 M)
Temperature:	40 °C
Time:	1.5 h for addition of diazoacetate and 30 min further.

General Notes on Performing Carbene C–H Insertion Reactions:

1. Many of the early work on these systems used 2,2-dimethylbutane as the solvent of choice. With more modern systems and for reasons of accessibility methylene chloride is now preferred. This switch in solvent does not, in general, significantly impact the reaction outcome.
2. All solvents involved should be thoroughly dried and degassed with argon. Adventitious water and oxygen can react with the carbenoids.
3. All reactions should be performed under an inert argon atmosphere, not nitrogen, as nitrogen can coordinate to the dirhodium complexes and reduce their efficacy.
4. Lower catalyst loadings than 1% are typically possible after optimization, but 1% is recommended when screening for efficacy in new reactions.
5. Recent advances in this area have focused on the nature of the ester group in the donor/acceptor carbenes. Substituting the methyl group with trihaloethanes has furnished robust systems with reduced side reactions.[64]

Recent Advances in Catalyst Design and their Impact on Selectivity

A key point of the above discussion is the paramount importance of substrate's stereoelectronic properties in the course of product formation. Indeed, in both intra- and intermolecular processes it is the presence of an activating group, intramolecular tethering, or whether the C–H bond is 1°, 2°, or 3° that is principal determinant of the site for carbene C–H insertion. Reliance on such factors for selectivity in C–H insertion has the consequence that such reactions are often not general, requiring substrate-specific optimization. As this significantly increases the barrier for applying this technique, particularly by nonexpert practitioners, there is a real need for more general and applicable processes. This need has driven the design of new catalyst architectures in recent years.

Surveying the extensive literature on the intermolecular insertion of carbenes into C–H bonds has allowed identification of trends dependent on the ligands that surround the dirhodium. Of particular importance for catalyst designers is the relationship between ligand steric presence and reaction at 1°, 2°, and 3°. As might be expected, the general rule of thumb for this relationship is that bulkier catalysts prefer less sterically crowded C–H bonds. However, this observation has been an imprecise guideline due to the dynamics and specific conformational details of the ligands that surround the catalyst during the insertion transition states and resolving this remains an active area of investigation. A recent advance in catalyst design, however, offers promising machinery to better survey and understand this relationship. With a ligand framework based on chiral tri-substituted cyclopropanes, the Rh_2(TPCP)$_4$ catalyst architecture offers a modular design that accelerates the design, synthesis and assessment of catalysts with varied, and to some extent, controlled steric arrangements. Members of this class of catalysts have already demonstrated exceptionally sensitivity to the steric environment of the substrate, able to select 1°, 3°, and even specific 2° C–H bonds of the same substrate based not on the inherent stereoelectronic properties of the reaction partner, but instead through catalyst identity.[65]

Undirected Sp^3: C–N Bond Formation

Given the ubiquity of Csp^3–N bonds in many important classes of molecules, methods leveraging the plethora of C-H bonds in organic molecules for the site-selective introduction of nitrogen atoms are of paramount importance.[66] Continuous study over the past two decades has furnished a range of methods that directly convert Csp^3–H bonds into C–N linkages using dirhodium paddlewheel complexes, often with high yields and tolerance for substrate functionality (**Figure 43**). From this, it is possible to aminate many substrates of interest to synthetic chemists, both in tethered, intramolecular and intermolecular senses. Many of the insights and trends described above for the dirhodium carbene insertion into C–H bonds are observed in these nitrene insertion reactions.

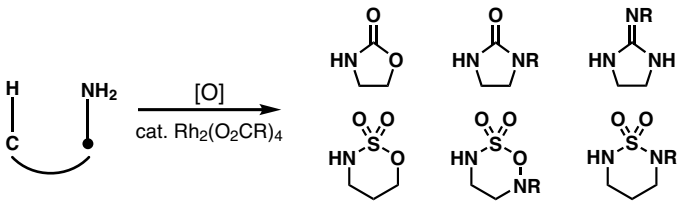


Figure 43. C–H Nitrene Insertion

Intramolecular Carbamate C–H Amination

The tethering carbamate group is accessible in 2 steps from alcohol starting materials (**Figure 44**).[67]

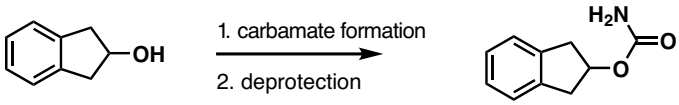


Figure 44. Carbamate Installation

Common Conditions

Solvent:	CH_2Cl_2 (0.3 M)
Reagents:	Cl_3CNCO (1.2 equiv.), then K_2CO_3 in CH_3OH (0.1 equiv.)
Temperature:	23 °C
Time:	2–6 h

This tethering group favors amination at C–H bonds adjacent to the alcohol-bearing carbon, resulting in 5-member cyclic carbamate products (**Figure 45**). These insertions occur in a stereospecific fashion due to the geometric constraints of the carbamate tether, with amination occurring in a syn fashion for cyclic substrates. Many rhodium tetracarboxylates are able to catalyze these reactions;[67] however, the strapped dicarboxylate $Rh(esp)_2$ has often exhibited higher stability during the course of the reaction, permitting low catalyst loadings that are not possible with the non-chelating acetate catalysts.[68] Additionally, the $Rh(esp)_2$ catalyst permits otherwise difficult aminations, such as those using the nitrogen-substituted homologues of carbonates, ureas and guanidines, to form 1,2-diaminated products.[69]

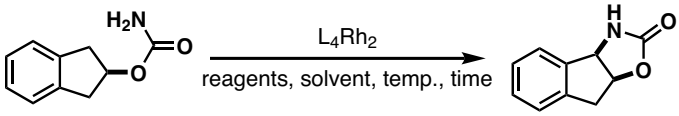


Figure 45. Intramolecular syn C–H Amination

Conditions A[67]

Solvent:	CH_2Cl_2 (0.2 M)
Rh2 Source:	$Rh_2(OAc)_4$ (5 mol %)
Reagents:	$PhI(OAc)_2$ (1.4 equiv.), MgO (2.3 equiv.)
Temperature:	40 °C
Time:	12 h

Conditions B (when low reactivity is observed with Conditions A):[67]

Solvent:	CH_2Cl_2 (0.2 M)
Rh2 Source:	$Rh_2(TPA)_4$ (5 mol %)
Reagents:	$PhI(OAc)_2$ (1.4 equiv.), MgO (2.3 equiv.)
Temperature:	40 °C
Time:	12 h

Conditions C

Solvent:	C_6H_6
Rh_2 Source:	$Rh_2(HNCOCF_3)_4$ (10 mol %)
Reagents:	$PhI(OAc)_2$ (1.4 equiv.), MgO (2.3 equiv.)
Temperature:	65 °C
Time:	12 h

Intramolecular Sulfamate C–H Amination

Sulfamate intramolecular tethering groups can also be prepared in a 2-step, 1-pot procedure from alcohol starting materials (**Figure 46**).[70]

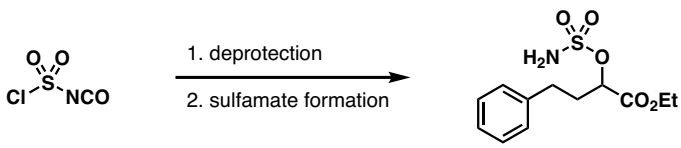


Figure 46. Sulfamate Installation

Common Conditions

Solvent:	CH_2Cl_2 (molarity changes over reaction)
Reagents:	$ClSO_2NCO$ (1.5 equiv.), formic acid (1.5 equiv.) then alcohol substrate (1 equiv.), pyridine (1 equiv.)
Temperature:	0 °C, upon addition of CH_2Cl_2 warm to 25 °C
Time:	11–13 h

The sulfamate tethering group favors C–H amination at carbon centers 2 atoms removed from the tethering alcohol carbon, resulting in 6-member cyclic sulfamate products (**Figure 47**).[41] These reactions are again stereospecific for cyclic alcohols due to geometry concerns and an enantioselective variant (using the dirhodium R- or S-NAP tetracarboxamidate,[71] Conditions D) is possible for open-chain sulfamates. Furthermore, it has been found that the C–O bond of the cyclic sulfamate products is activated toward displacement by a variety of nucleophiles, providing a means of rapidly assembling 1,3-amine-nucleophile dyads from simple alcohol starting materials.[70] Similarly, sulfamates derived from phenols can subsequently be engaged in Kumada-Corriu reactions using nickel catalysis.[72]

An interesting further opportunity for sulfamate elaboration is encountered upon insertion of the metal nitrene into ethereal C–H bonds, resulting in the formation of a hemiaminal ether.[73] This reactive species serves as a latent iminium electrophile, allowing for the alcohol fragment to be substituted with a variety of nucleophiles under mild conditions.

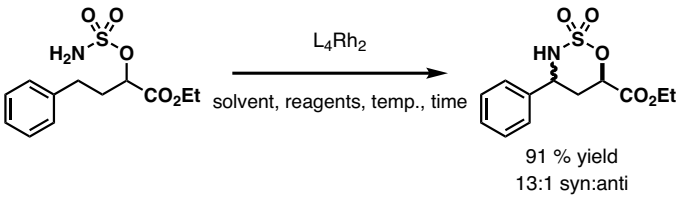


Figure 47. Intramolecular Sulfamate C–H Amination

Conditions A[70]

Solvent:	CH_2Cl_2 (0.16 M)
L_4Rh_2 Source:	$Rh_2(OAc)_4$ (2–5 mol %)
Reagents:	sulfamate substrate (1.0 equiv.), $PhI(OAc)_2$ (1.1 equiv.), MgO (2.3 equiv.)
Temperature:	40 °C
Time:	2 h

Conditions B[70]

Solvent:	CH_2Cl_2 (0.16 M)
L_4Rh_2 Source:	$Rh_2(oct)_4$ (2–5 mol %)
Reagents:	sulfamate substrate (1.0 equiv.), $PhI(OAc)_2$ (1.1 equiv.), MgO (2.3 equiv.)
Temperature:	40 °C
Time:	2 h

Conditions C[68]

Solvent:	*i*-PrOAc (0.1 M)
L_4Rh_2 Source:	$Rh_2(esp)_2$ (2 mol %)
Reagents:	sulfamate substrate (1.0 equiv.), $PhI(OAc)_2$ (1.1 equiv.), MgO (2.3 equiv.)
Temperature:	23 °C
Time:	4 h

Conditions D[71] (enantioselective)

Solvent:	CH_2Cl_2 (0.5 M)
L_4Rh_2 Source:	$Rh_2(S\text{-}nap)_4$ (2 mol %)
Reagents:	sulfamate substrate (1.0 equiv.), PhI=O (1.2 equiv.), 3Å molecular sieves (powdered, 530 mg/mmol substrate)
Temperature:	23 °C
Time:	2 h

Finally, the nitrogen-containing tether sulfamide can be generated from amide starting materials and used to directly generate the cyclic sulfamides of 1,3-diamines.[74]

General Notes on Performing C–H Amination Reactions:

1. Oxidant should be added last to a vigorously stirring reaction mixture at room temperature.
2. Fine MgO should be flame- or oven-dried before use.
3. $PhI(OAc)_2$ can be substituted with other I^{III}-dicarboxylate oxidants (OPiv, OTFA, etc.)
4. Reactions usually turn from green to red upon the addition of oxidant (Rh^{II}–Rh^{II} → Rh^{II}–Rh^{III})
5. Reactions can range from red-orange to green upon completion depending on the state of the catalyst

Substrate Considerations:

- The reaction is stereospecific and stereoretentive for stereogenic C–H bonds.
- Sulfamate and sulfamide tethers prefer to form 6-membered rings.
- Carbamate, urea, and guanidine tethers prefer to form 5-membered rings.
- Generally, for yield and general reaction efficiency: sulfamate > carbamate > urea, guanidine.
- Substrates that work best for this chemistry contain 3°, benzylic, or α-heteroatom (N,O) C–H bonds
- Allylic C–H bonds tend to give mixtures of aziridination and C–H amination

Intermolecular Sulfamate C–H Amination

In recent work, the Du Bois group discloses a new set of intermolecular sp^3 C–H amination conditions utilizing pivalonitrile as solvent with greatly improved performance on a wide variety of complex molecule substrates, including numerous natural product and API derivatives (**Figure 48**).[75]

The reaction is insensitive to air and moisture and does not require drying of solvent for optimal performance. In addition to tolerating common functionality and valuable synthetic handles such as pinacol boronate esters, heteroaryl bromides, electron rich arenes, oxadiazoles and some unprotected secondary alcohols, the reaction generally provides excellent mass balance, allowing for intact recovery of high-value substrates which do not proceed to completion. Product sulfamates are easily unmasked to the corresponding primary amines by heating with pyridine in wet acetonitrile while also tolerating other hydrolytically sensitive functionality.

Though the exact mechanism by which pivalonitrile is enhancing performance remains elusive, mechanistic investigations suggest that catalyst lifetime is significantly prolonged in pivalonitrile compared to other solvents tested. Additionally, solvent oxidation was found to have a marked role on catalyst performance as use of deuterated acetonitrile nearly doubled turnover seen in standard acetonitrile. Current efforts focus on further understanding mechanisms of catalyst arrest with the express goal of improving catalyst turnover.[76]

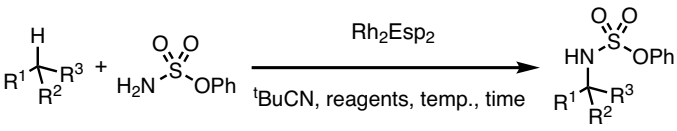


Figure 48. Intermolecular Sulfamate C–H Amination

Conditions:

Solvent:	^{t}BuCN (1.0 M)
L_4Rh_2 Source:	$Rh_2(esp)_2$ (1 mol %)
Reagents:	phenyl sulfamate (1.3 equiv.), $PhI(OPiv)_2$ (1.5 equiv.), Al_2O_3 (4 equiv.)
Temperature:	20 °C
Time:	6 h (longer reaction times not detrimental)

General notes on performing intermolecular amination reaction:

- Anhydrous ^{t}BuCN is not required. If ^{t}BuCN appears slightly yellow, it can be decolorized by passing through a short plug of grade I basic alumina.
- Oven dried alumina is unnecessary, and α-, β-, γ-phases of alumina all seem to perform similarly
- For optimal results, all reagents except $PhI(OPiv)_2$ should be stirred together until a deep navy blue color is observed (color indicates dissolved $[Rh_2(esp)_2]$ $(^t BuCN)_2$). Strongly coordinating substrates such as amides often initially appear purple, but with sufficient pre-stirring (10–40 min), the navy color will appear.
- Other I^{III} oxidants (OAc, OTFA) can be used, but with diminished performance.
- Reactions typically progress from navy to brick red upon addition of oxidant
- Poorly performing substrates (<10% amination) often blanch to pale yellow within 10–15 minutes of reaction.
- Sulfamate products readily unmasked to primary amines

Substrate Considerations:

- Reaction is stereospecific and stereoretentive for stereogenic C–H bonds. Moderate to highly diastereoselective amination is observed when substrate has proximal stereocenters
- Aziridination is favored over allylic C–H amination under the reaction conditions
- If a substrate contains sterically accessible benzylic or 3° C–H bonds, those sites will tend to be preferentially aminated, though proximity to electron-withdrawing functionality can disfavor an otherwise reactive site
- Relative electronics (and thus reactivity) of equisteric pairs of 2° (or 3°) sites can be approximated by ^{13}C NMR shift

Notes on preparation of phenyl sulfamate:

When preparing phenyl sulfamate, best results are achieved when the generation of sulfamoyl chloride is allowed to stir for 5 hours instead of the stated 2 hours to ensure complete decomposition of the intermediate O-formyl carbamate intermediate to CO_2 and CO.[77] Additionally, slow addition (ca. 1 mL/min for described 39 mmol scale) of phenol in DMA is crucial for reproduceable yields of the sulfamate. After workup, rotary evaporation from heptane followed by drying under high vacuum can remove traces of phenol or DMA present in product.

Undirected C–H Hydroxylation

The selective oxidation of C–H bonds to produce hydroxyl and carbonyl functional groups is an important C–H functionalization reaction in both enzymatic systems and synthetic chemistry labs. While the difficult problem of achieving regioselectivity for a specific bond within a molecule has been tackled using innovative catalyst design and directing groups (for an example of this please see the directed, non-organometallic reactions section of this guide), an equally important consideration is that of chemoselectivity among functional groups. Nitrogenous functional groups (e.g., amines, pyridines, imines) in particular are susceptible to oxidation and compete with C–H oxidation under many oxidative reaction conditions. This challenge has traditionally precluded the use of many nitrogen-containing functional groups in C–H oxidation protocols.

A recent, collaborative advance from the Du Bois and Sigman groups has provided a means of overcoming this side reactivity through the synergistic use of a strong acid additive with a well-defined ruthenium precatalyst that is stable to acidic aqueous conditions (**Figure 49**).[78] The strong acid protonates Lewis basic nitrogen sites, depleting their electron density and thus deactivating them to oxidation. Further, this protonation discourages oxidation of proximal C–H bonds, permitting remarkable selectivity for distal C–H bonds to be observed for many substrates. Successful chemoselective C–H oxidation was demonstrated with a number of common nitrogen-based functional groups; moderate to high yields were obtained for benzylic or tertiary C–H bonds that are sufficiently remote from the transient ammonium ion formed under the acidic conditions.

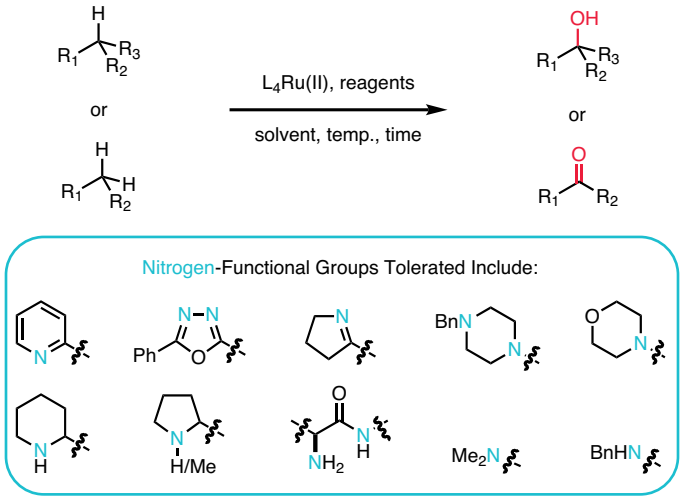


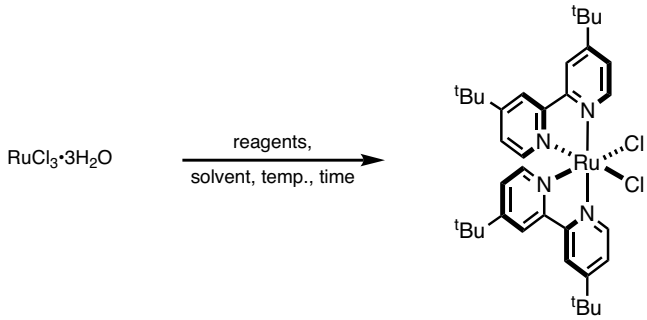
Figure 49. Amine Tolerant Undirected C–H Hydroxylation

Conditions:	
Solvent:	1:1 AcOH/H_2O (0.07 M)
Ru(II) Source:	cis-[$Ru(dtbpy)_2Cl_2$] (5 mol %)
Reagents:	substrate (1.0 equiv.), TfOH (6.0 equiv.), H_5IO_6 (2.0 equiv.)
Temperature:	23 °C
Time:	4 h

Reaction Notes:

1. cis-[$Ru(dtbpy)_2Cl_2$] can be substituted with commercial cis-[$Ru(bpy)_2Cl_2$]; however, in general the observed yield is half that obtained using the di-tert-butyl analogue.
2. TfOH can be replaced with other strong acid additives (H_2SO_4, CF_3CO_2H, or CH_3SO_3H) with minimal effect on yield.
3. H_5IO_6 can be substituted with other terminal oxidants [$NaIO_4$, $KBrO_3$, or $Ce(NO_3)_6(NH_4)_2$] with minimal effect on yield.

Catalyst Preparation[79]



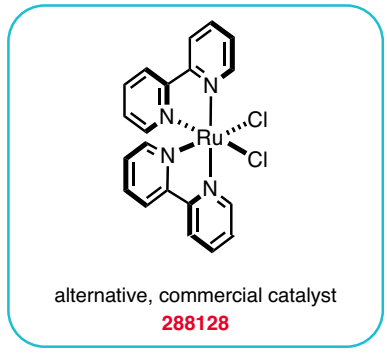


Figure 50. Preparation of cis-[$Ru(dtbpy)_2Cl_2$]

Conditions:	
Solvent:	DMF (0.5 M)
Ru(II) Source:	$RuCl_3 \bullet 3H_2O$ (1.0 equiv.)
Reagents:	dtbpy (2.0 equiv.), LiCl (0.7 equiv.)
Temperature:	reflux
Time:	6 h

Substrate considerations:

- The strong acid additive can be omitted in cases where basic functionalities do not need to be deactivated via protonation; comparable yields are obtained both with and without acid in these cases.
- If working with an acid-labile substrate, MeCN can be substituted for AcOH with little or no effect on the reaction outcome. It is however important to note that H_5IO_6 does not perform in this solvent mixture, and one of $NaIO_4$, $KBrO_3$, or $Ce(NO_3)_6(NH_4)_2$ should be used instead.
- In general, basic functional groups whose conjugate acids possess a pKa approaching or below 1 are not anticipated to protonate to a sufficient extent to be protected from oxidation. However, substrates containing cyclic imines and a 1,3,4-oxadiazole can still provide products of remote oxidation.
- Functional groups that are generally not compatible with this chemistry include electron-neutral or -rich arenes (including anilines), olefins, and alkynes. *N*-alkyl imidazoles dealkylate selectively, and ethers will be oxidized to the corresponding ester.
- Substrates that will work best with this chemistry contain sterically accessible tertiary or benzylic C–H bonds. Pursuant to the previous discussion of HAT selectivity, C–H bonds further removed from strongly electron-withdrawing protonated amine positions will oxidize in preference to those that are closer. In general, the best yields are seen in substrates where the desired site of oxidation is separated from the ammonium nitrogen by 4 or more bonds. While this reactivity trend and that of a related system suggest that a HAT/radical rebound process may be operative,[80] the mechanism of C–H hydroxylation using this system is a current area of study.

Undirected Radical Methods

Open shell, radical processes have long presented an important complement to 2-electron ionic reactions,[81] and this is especially true for the field of C–H functionalization.[82] Both radical addition reactions to aromatic systems and hydrogen atom abstraction reactions have provided means of selectively functionalizing C–H bonds that would be difficult, if not impossible, to achieve using organometallic methods, ultimately generating useful complexity for synthetic chemists.

Radical Philicity: A Useful Tool for Understanding Radical-Based C–H Functionalization

Much like ionic reactions are favored with polarity matching, such as when an electron-deficient electrophile is paired with an electron rich nucleophile in a substitution reaction, radical methods proceed most readily when a radical of either electron excessive (nucleophilic) or deficient (electrophilic) character reacts with a partner of opposite polarity.[83] This analysis is important for both radical substitution reactions, such as the Minisci reaction,[84] and hydrogen atom transfer (HAT) C–H activation processes.[85]

Qualitatively determining the polarity of a radical can be achieved through comparing the stabilities of its cation (formed by removing 1 electron) and anion (formed through contributing 1 electron) using the same arguments of conjugation, hyperconjugation, and inductive effects as taught in undergraduate organic chemistry (**Figure 51**). Cases where the cation is more stabilized are electron excessive and, thus, nucleophilic while those favoring the anion are electron deficient, or electrophilic. For example, from this analysis it is shown that simple alkyl radicals are nucleophilic in character, while enol radicals are electrophilic.

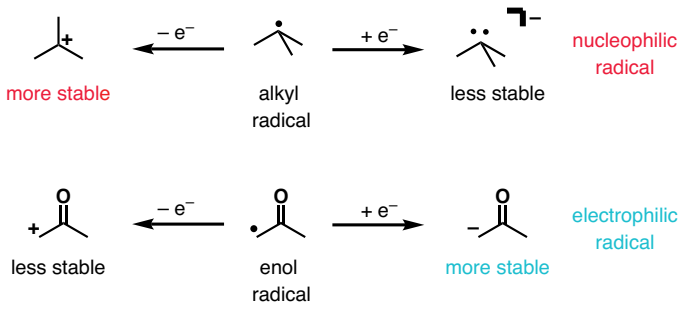


Figure 51. Nucleophilic and Electrophilic Radicals

Similarly analyzing the partial charges of radical addition partners (e.g., olefins) reveals them to have nucleophilic and/or electrophilic sites. As stated above, nucleophilic radicals will favor addition to electrophilic sites while electrophilic ones will favor vice versa. Importantly, the same molecule might have multiple sites of either nucleophilic or electrophilic character, allowing prediction of the selectivity of radical addition based on the polarity of the radical reagent.

Similar to the radicals themselves, C–H bonds can be roughly classified as electron excessive and electron deficient based on the relative stability of their hydride abstraction and deprotonation products (cation and anion, respectively). Cases where the cation is expected to be more stable are electron rich while those favoring the anion are electron deficient. Hydrogen atom abstractors also favor polarity matching, meaning that all else being equal, there will be a preference for an electrophilic radical to react with a more electron-rich C–H bond. This effect becomes important in the HAT section below.

Undirected Sp^2: Radical-Based Methods

The successful application and selectivity of radical additions to sp^2 centers can generally be predicted by considering the relative polarity of both the radical and its acceptor. As discussed above, radical polarity matching can have a large effect on rate and selectivity of radical C–H functionalization reactions, of which the Minisci reaction,[84,86] or the substitution of aromatic systems using radical intermediates, is an important example.[87] When imagining what radical partners to functionalize a sp^2 site with, it becomes clear that many of these (e.g., alkyl, aryl, etc.) can be considered "nucleophilic", or electron-excess radicals. As a result, these species will most readily react with electrophilic π systems at their most electron-deficient sites. In the case of the Minisci reaction, this polarity argument results in effectively anti-Friedel-Crafts selectivity: electron deficient heteroarenes react more readily than electron rich arenes and addition is often to the site least able to stabilize positive charge.

In Minisci-type additions to nitrogen-containing electron deficient heteroarenes, it has often been observed that selectivity and reactivity can be enhanced by coordinating a Lewis acid to the nitrogen atom, further removing electron density from the ring. Proton is often sufficient for these purposes, with simply lowering the pH of the reaction mixture resulting in dramatically improved selectivities and rates.[84]

However, while these two exercises can enable generally acceptable application of the Minisci retron, it should be noted that selectivity of these reactions can also be modulated by many other factors,[86] especially solvent composition. Thus, it is key to adequately explore these reaction variables in order to achieve their desired selectivity. To enable this, we have provided a flow chart to help design appropriate conditions for a desired Minisci functionalization reaction (**Figure 52**).

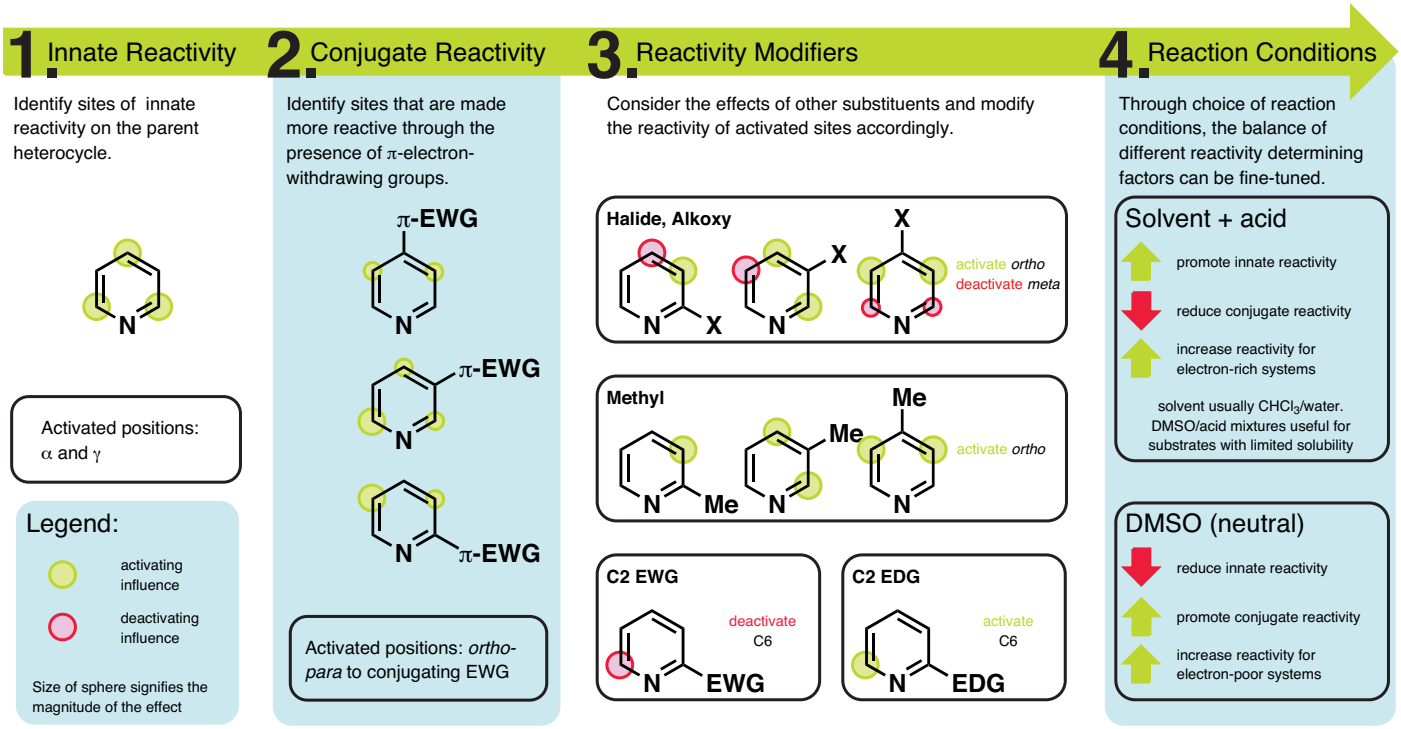


Figure 52. Flow Chart for Minisci Functionalization Reaction Design

Common Conditions

Solvent:	$H_2O/CHCl_3$
Radical Precursor:	zinc sulfinate ("diversinate" reagent)
Oxidant:	tert-butyl hydroperoxide (TBHP)
Time:	2 h

Undirected Sp³: Radical-Based Methods (PCET/HAT)

Proton-Coupled Electron Transfer (PCET) and Hydrogen Atom Transfer (HAT, also called hydrogen atom abstraction), when applied in C–H activation, are mechanisms that result in the homolytic cleavage of C–H bonds to transiently generate carbon centered radical reactive intermediates.[88] These radicals can then be engaged in any number of functionalization steps,[81a] including hydroxylation,[89] fluorination,[90] alkylation,[91] and arylation.[87] These transformations often occupy a complementary space to the aforementioned organometallic methods as they can provide different selectivity profiles (e.g., alkylation) or, in some cases, permit functionalizations that are still challenging to organometallic approaches (e.g., fluorination).[92]

PCET/HAT processes are common when using catalysts or reagents with radical character and proceed through non-organometallic C–H activation pathways, or mechanisms where C–H bond cleavage does not result in the formation of a catalyst or reagent metal–carbon bond.[93] Indeed, while metal oxo's are well known effectors of this mechanism, metals need not be involved in PCET/HAT processes as oxygen-centered radicals and photoexcited ketones are also common reagents for these transformations.[94] As these represent a dramatically different activation mechanism than that found in the aforementioned CMD or direct insertion pathways, it is unsurprising that their selectivity rules are significantly different and merit individual study.

Three main factors usually dominate the ultimate selectivity: 1) bond energies of the C–H bond in the substrate and quenched abstractor; 2) relative polarity of both the substrate and the abstracting species; and 3) the number of equivalent C–H bonds in the substrate.

1. A useful first analysis to perform when applying PCET/HAT activation processes to a molecule of interest is the thermodynamic driving force of the net reaction. Aside from showing whether there exists a driving force for the forward activation event (a necessary stipulation for a reaction to occur) it has also been found that the activation energy of the C–H cleavage event can (but does not always) correlate with the overall free energy of the process.[8] From this quality we can get two general guidelines for evaluating simple PCET/HAT activations:

   a. HAT will usually occur readily only if the strength of the new abstractor–hydrogen bond is more than that of the C–H bond that was cleaved (**Figure 53**). Therefore, knowing the bond strength of the quenched abstractor allows for prediction of the strongest bond that could be activated, giving a measure of control over which bonds will be addressed via changing the abstracting species. For reference, a table of C–H bond dissociation energies has been included in this guide (see Appendix A), along with some relevant bond strengths of quenched abstracting species.

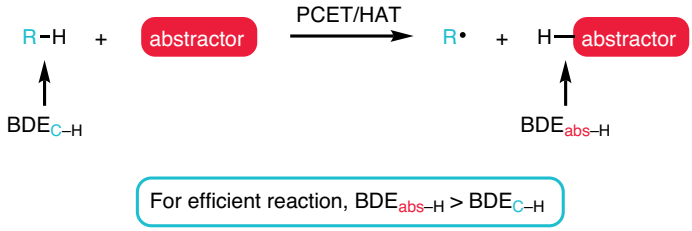


Figure 53. PCET and HAT Governed by BDE

   b. In the absence of directing or polar effects, HAT will usually proceed first and fastest with the weakest C–H bond that is within the abstraction ability of the catalyst (see above). From this, prediction of the first site of functionalization of a molecule can often (but not always) be determined simply by bond strength analysis (**Figure 54**).

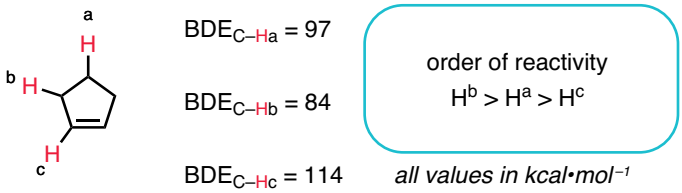


Figure 54. HAT Reactivity Trend

   However, this simple thermodynamic analysis, while powerful, is often tempered by other molecular properties that can modulate the rate and, thus, selectivity of the reaction.

2. While there are several additional considerations that can affect selectivity, including molecular strain and stereoelectronic effects,[85] polarity, as discussed above, is among the most useful to consider along with thermodynamics when planning HAT reactions. PCET/HAT methods often favor cases where the polarity of the abstracting species matches that of the hydrogen donor species.

   In practice, as many C–H bonds can be considered electron rich (their homolyses produce nucleophilic radicals), many successful abstracting species are electron deficient. Therefore, more "electron rich" C–H bonds can react in preference to weaker, though more "electron poor" C–H bonds when using common abstractors. An interesting example is provided by the cumyloxy radical's rates of reaction (corrected for number of degenerate C–H bonds) for abstracting the C–H bonds from cyclohexane, a common C–H functionalization test substrate, and acetonitrile, a solvent that has been used in C–H functionalization reactions. Interestingly, cyclohexane is at least 30 times more reactive than acetonitrile,[95,96] despite having a weaker bond energy (99.5 vs 97.0 kcal•mol^{-1}, **Figure 55**).[97]

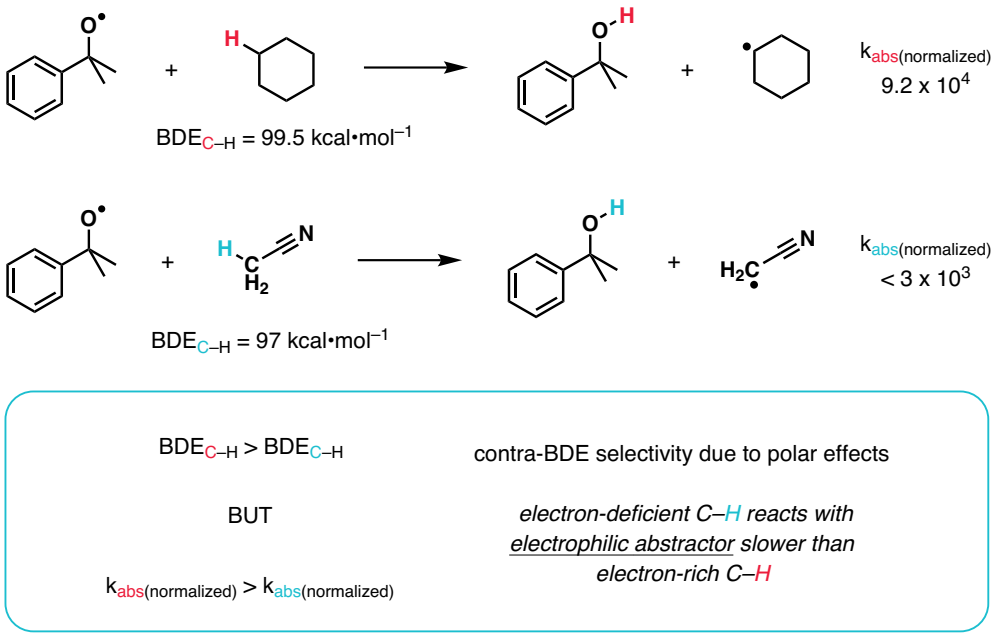


Figure 55. Cyclohexane vs. Acetonitrile in HAT

An important stipulation for applying a PCET/HAT retron in a synthesis is to reevaluate the polarity of the C–H bonds in the product following the C–H functionalization event. If the polarity of the remaining C–H bonds has not been changed significantly or has been made a better match for the abstractor compared to the starting material, it may be difficult or impossible to perform monofunctionalization reactions due to further reaction of the product. From this, C–H oxidation reactions (e.g., oxygenation, fluorination) are among the most popular applications of the PCET/HAT manifold using electrophilic abstractors, as introduction of inductively withdrawing functionality reduces the electron density on the remaining C–H bonds, deactivating the product relative to the starting material.

An example showing both the effect of polarity on initial reaction with a substrate and subsequent deactivation of the product toward further reaction is provided by the photocatalytic fluorination of C–H bonds using tetra-*n*-butylammonium decatungstate (TBADT) (**Figure 56**).[90] While the C–H bond adjacent to the ester carbonyl of methyl 4-methylvalerate is expected to be weakest and most susceptible to PCET/HAT activation, TBADT, a catalyst whose photoexcited state is electrophilic in character, selects for the stronger, yet also more electron-rich 3° C–H. Following quenching of the radical with NFSI, the remaining C–H bonds in the product are protected from further reaction by the combined inductive effects of the ester and fluoride to render them inert, ultimately furnishing a single alkyl fluoride compound.

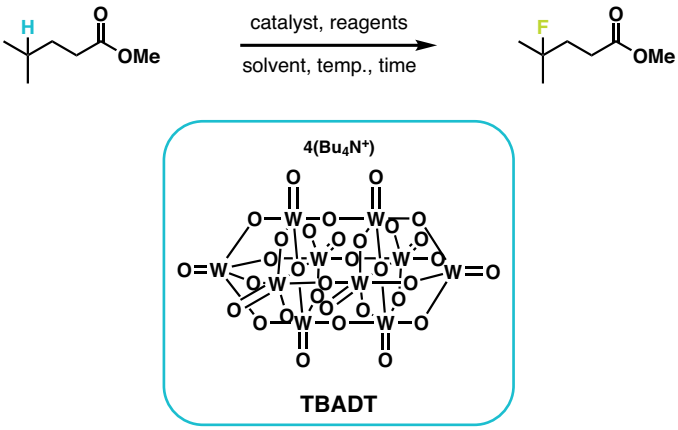


Figure 56. Photocatalytic Fluorination

Common Conditions

Solvent:	MeCN (1–2 M)
Catalyst:	tetra-*n*-butylammonium decatungstate (TBADT) (2 mol %)
Reagents:	*N*-fluorobenzenesulfonimide (NFSI) (1.5 equiv.), $NaHCO_3$ (0.1 equiv.)
Oxidant:	*tert*-butyl hydroperoxide (TBHP)
Temperature:	23 °C
Time:	16 h

Notes: irradiated with 365 nm light, under an inert atmosphere.

3. Finally, statistics should always be considered when predicting the outcome of HAT reactions. While the bond strength and polarity of a given C–H bond will largely determine its intrinsic reactivity with an abstracting species, the relative concentration of each chemically similar C–H bond can also affect the ultimate product ratio, especially for highly reactive abstracting species. This is done for the cumene oxyl example above, where the acetonitrile and cyclohexane rates have been corrected for 3 and 12 equivalent C–H bonds, respectively.

   Using these three principles, it's possible to arrive at a reasonable prediction of how a given molecule might react under nondirected PCET/HAT conditions.

Product Tables

Oxidants

Product Description	Cat. No.
$PhI(OAc)_2$	178721
$PhI(OAc)_2$ (0.5 M in DCM)	902772
H_2O_2	516813
H_5IO_6	375810
$PhI(OPiv)_2$	662283
TBHP	458139
1-Fluoro-2,4,6-trimethylpyridinium tetrafluoroborate	439312
1-Fluoro-2,4,6-trimethylpyridinium triflate	738115
MnF_3	339296
Potassium persulfate	216224
F-TEDA	439479
AgOAc	204374

Catalysts

Product Description	Cat. No.
$Pd(OAc)_2$	520764
$RuH_2(CO)(PPh_3)_3$	335002
$Ru_3(CO)_{12}$	245011
$[Cp^*RhCl_2]_2$	338370
$[(p\text{-cymene})RuCl_2]_2$	683213
$[IrCl(COD)]_2$	683094
$[IrOMe(COD)]_2$	685062
$Rh_2(S\text{-DOSP})_4$	470449
$Rh_2(OAc)_4$	482285
$Rh_2(TPA)_4$	725455
$Rh_2(oct)_4$	442100
$Rh_2(esp)_2$	662623
cis$[Ru(bpy)_2Cl_2]$	288128
$RuCl_3.3H_2O$	10452
TBADT	900432
Iron(III) phthalocyanine chloride	379573
MCAT-53™	900285
$Pd(OPiv)_2$	721611
$Pd(TFA)_2$	299685
PCy_3 Pd G2	756741
$RuCl_2(PPh_3)_3$	223662

Directing Groups and Auxiliaries

Product Description	Cat. No.
8-Aminoquinoline	260789
Yu-Wasa Auxiliary	791806
2-Picolinic acid	P42800
$NH_2OH•HCl$	255580
2,2′-Azanediyldibenzonitrile	L511269
N,N′-(2,3-Dimethylbutane-2,3-diyl)bis(pyridine-3-sulfonamide)	900718
2-Hydroxynicotinaldehyde	ALD00594
Li-Li Auxiliary	900583
2-(Pyridin-2-yl)isopropyl amine	802166
Tanaka-Yu template	900719
Tang-Yu Auxiliary	791369
Zhu-Yu Auxiliary	ALD00600
[2,2′-Bipyridine]-6-carboxylic acid hydrochloride	901251
2-(Pyridin-2-yl)quinolin-8-amine dihydrochloride	901250

Ligands

Product Description	Cat. No.
3-Acetylamino-2-hydroxy-5-(trifluoromethyl)pyridine	ALD01834
N-((*S*)-1-((4*S*,5*S*)-4-Benzyl-5-phenyl-4,5-dihydrooxazol-2-yl)-2,2-dimethylpropyl)acetamide	900715
N-((*S*)-1-((*S*)-4-Benzyl-4,5-dihydrooxazol-2-yl)-2,2-dimethylpropyl)acetamide	900714
CF_3-dba	ALD00382
2-Carbomethoxynorbornene	ALD00510
N-((1*S*,2*S*)-1-(3,5-Di-*tert*-butylphenyl)-2-(quinolin-2-yl)butyl)acetamide	ALD00596
Li-Quinoline Ligand	ALD00002
Li-Yu t-Butyl Quinoline	ALD00004
(*S*)-Ph-quinox	901216
Shi-Yu MPAA Ligand	ALD00376
3,4,7,8-Tetramethyl-1,10-phenanthroline	162884
Wasa-Yu MPAA Ligand	ALD00378
Yu Borylation Ligand	ALD00506
Yu Fluorination Ligand	ALD00508
1-Heptyl-2-norbornene	903647
1-Cyclohexyl-2-norbornene	903655
1-Isopropyl-4-methyl-5-norbornene	903698
N-((1*S*,2*S*)-1-((*R*)-4-Isopropyl-4,5-dihydrooxazol-2-yl)-2-methylbutyl)acetamide	900717
N-((1*S*,2*S*)-1-((*R*)-4-Isobutyl-4,5-dihydrooxazol-2-yl)-2-methylbutyl)acetamide	901417
N-((1*S*,2*S*)-1-((*S*)-4-Isobutyl-4,5-dihydrooxazol-2-yl)-2-methylbutyl)acetamide	901419
Wang-Yu Pyridone Ligand	ALD00606

Baran Diversinates™

Product Description	Cat. No.
Sodium 2-(2-bromophenyl)-1,1-difluoroethanesulfinate	ALD00462
Sodium *N*-benzyloxycarbonyl-4-piperidinesulfinate	ALD00456
Sodium 2-(3-bromophenyl)-1,1-difluoroethanesulfinate	ALD00458
Sodium 7-chloro-1,1-difluoroheptane-1-sulfinate	ALD00484
Sodium *tert*-butylsulfinate	ALD00288
Sodium 4,4-difluorocyclohexanesulfinate	ALD00230
Sodium 1,1-difluoroethanesulfinate	745405
Sodium difluoroheptylazidosulfinate	746118
Sodium isopropylsulfinate	ALD00440
Sodium 1,1-difluoro-4-(2-methyl-1,3-dioxolan-2-yl) butane-1-sulfinate	792446
Sodium 2,2-dimethylpropylsulfinate	ALD00290
Sodium ethylsulfinate	ALD00294
Sodium tetrahydrofuransulfinate	ALD00234
Sodium tetrahydropyransulfinate	ALD00232
Sodium 1-(trifluoromethyl)cyclopropanesulfinate	790184
Sodium trifluoropropylsulfinate	ALD00238
Sodium (4-bromophenyl)methanesulfinate	ALD00476
Sodium 2-naphthalenemethanesulfinate	809098
Sodium 1-phenoxy-methanesulfinate	809063
Sodium 2-methylcyclopropylsulfinate	900635
Sodium 2-(3-oxetane)propylsulfinate	900630
Zinc benzylsulfinate	790796
Zinc bis[(phenylsulfonyl)methanesulfinate]	792187
Zinc chloroethanesulfinate	790788
Zinc chloromethanesulfinate	791105
Zinc difluoromethanesulfinate	767840
Zinc isopropylsulfinate	745480
Zinc *n*-propylsulfinate	791040
Zinc trifluoroethanesulfinate	745499
Zinc trifluoromethanesulfinate	771406

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Appendix A: Bond Dissociation Energies of C–H Bonds

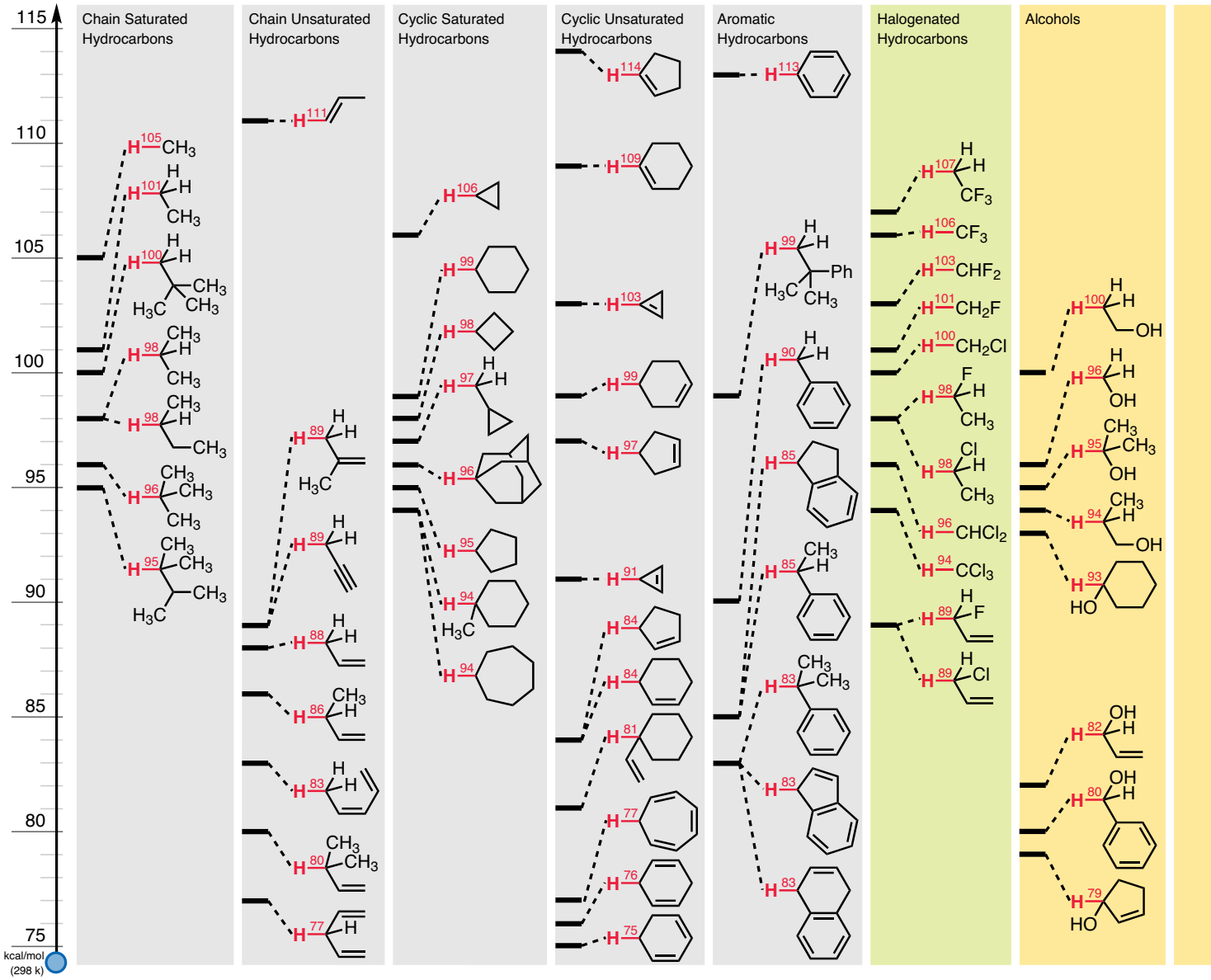
Bond Dissociation Energies of C–H Bonds in Common Organic Molecular Frameworks

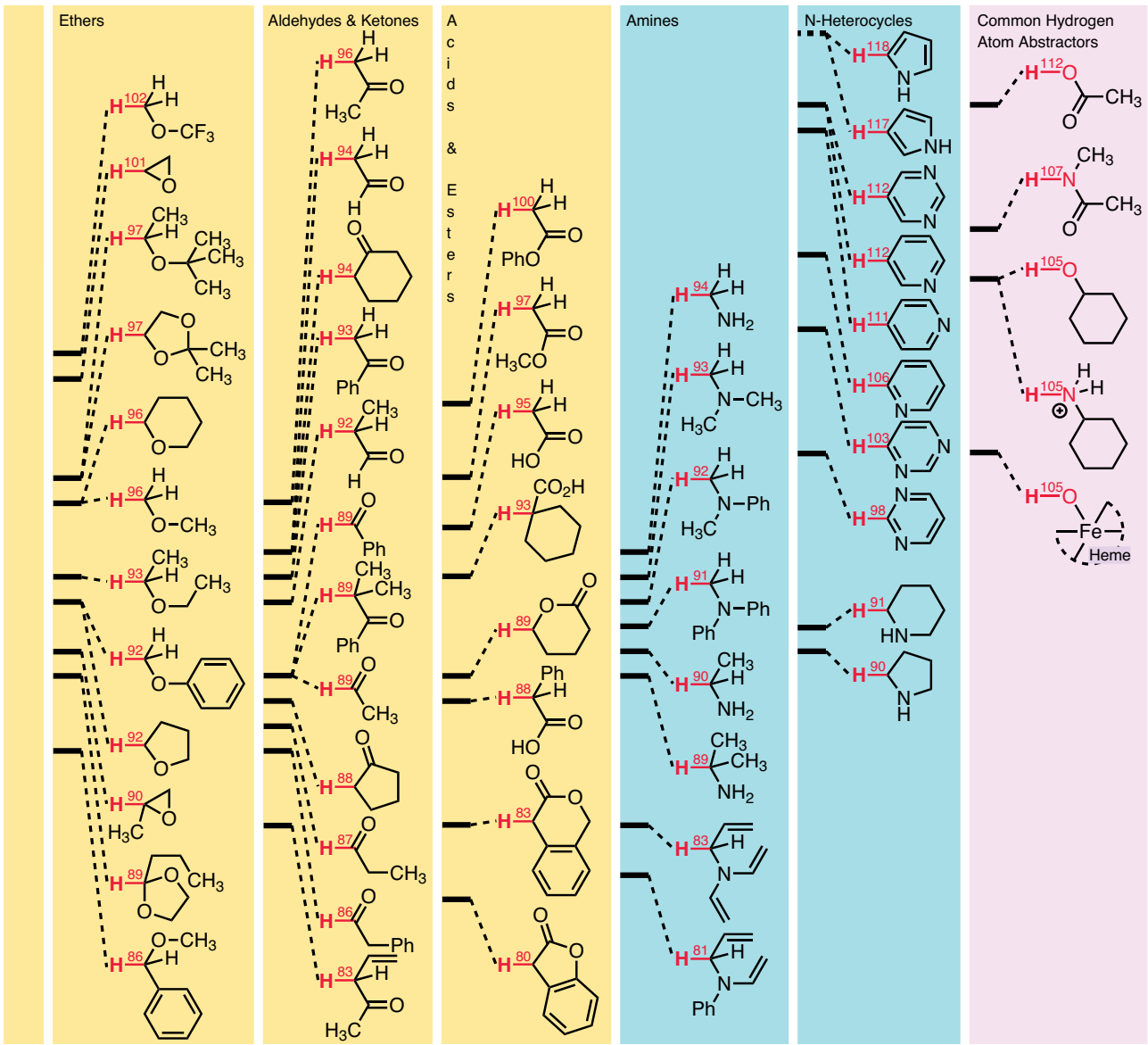
Summarized here are the bond dissociation energies of C–H bonds found in many common structural motifs.

Due to the ubiquity of C–H bonds in organic molecules an exhaustive survey is impossible, rather examples have been chosen to illustrate important trends across chemical skeletons.

The final panel shows the energies of functionalities commonly employed as Hydrogen Atom Abstractors.

Information gathered from: Comprehensive Handbook of Chemical Bond Energies, Yu-Ran Luo, CRC Press, 2007, p19-134; ISBN: 9780849373664

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Behind the Manual

We have long partnered with the scientists in the field to support their explorations by sharing knowledge, providing educational resources, and being a reliable supplier of cutting-edge materials. This manual was developed in collaboration with chemists from the Center for Selective C-H Functionalization (CCHF) with the intent of lowering the barrier for applying these reactions in the laboratory.

This resource for the practicing organic chemist should help in developing shorter, more efficient, and more insightful synthetic routes. You'll find reactivity trends and important examples of C–H functionalization paired with practical commentary.

The CCHF's mission is to develop technology for selective C–H functionalization that will revolutionize the practice and reshape the teaching of chemical synthesis, empowering end users in the material sciences, fine chemicals development, and drug discovery. The center, a National Science Foundation Center for Chemical Innovation, has taken a leading role in the development, application, and mechanistic interrogation of new C–H functionalization methods. Its members also work to educate practitioners and support the uptake of its technology.

When possible, this manual refers to commercially available components. We are proud to foster collaborations with developers and practitioners in the field to provide the necessary Sigma-Aldrich® reagents and catalysts for C–H functionalization reactions.

Main Contributors:

Dr. Julian G. West was born in Salt Lake City, UT and raised in Edmonton, AB, Canada. He received his BS (Hons.) in 2013 from the University of British Columbia, Vancouver, supervised by Prof. Glenn M. Sammis. He then undertook PhD studies under the mentorship of Prof. Erik J. Sorensen and was an active member of the NSF-CCHF throughout his graduate career, studying photocatalytic methods for C–H functionalization. After defending in 2017, Julian began postdoctoral studies at the California Institute of Technology under the joint advisement of Profs. Harry B. Gray and Brian M. Stoltz. Outside of chemistry, he is an amateur, though passionate, maker of- and listener to- music.

Dr. Daniel Morton received his M.Chem. degree in Chemistry from the University of East Anglia and stayed to pursue his PhD in synthetic organic chemistry under the guidance of Profs. Robert Stockman and Robert Field. In 2005, he joined the group of Prof. Adam Nelson at the University of Leeds, performing postdoctoral studies in total synthesis and diversity-oriented synthesis. In 2008, he moved to the group of Prof. Huw Davies at Emory University, exploring dirhodium-catalyzed O–H and C–H insertion chemistry. In 2011, he took a position at Chirotech, part of Dr. Reddy's. As of 2013, he is back at Emory as the managing director of the CCHF.

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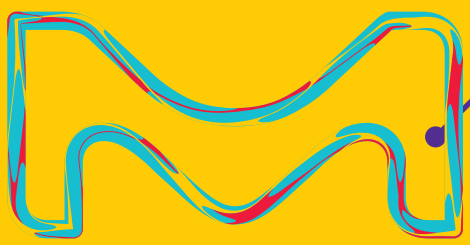

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